The fate, survival and suitability for definitive surgery of infants with double inlet ventricle and tricuspid atresia

By

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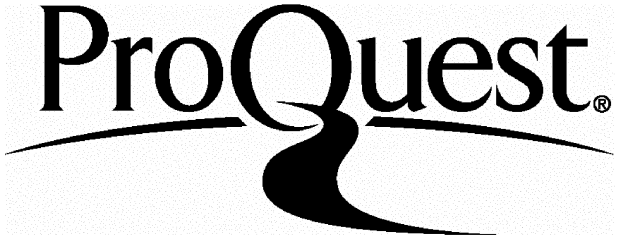

Abstract

Definitive surgery by Fontan-type surgery is regarded as optimal long term treatment for children with functionally a univentricular heart, such as double inlet ventricle and tricuspid atresia. Most patients with such complex congenital heart disease require palliative surgery to survive beyond infancy with suitable anatomy and physiology for definitive surgery. The influences on these parameters of different management strategies undertaken in infancy are crucial, but have not been studied in an unselected population in the Fontan era. This thesis addresses these issues and evaluates the effectiveness of management strategies in achieving suitability for a successful definitive repair. A retrospective study was undertaken by examining patient records of 428 unselected consecutive infants (1972-87): 191 with double inlet ventricle and 237 with tricuspid atresia. The previously unknown full morphological spectrum of the two lesions when presenting in infancy are detailed. Time related survival for the patient sub-groups using different management strategies were determined and compared. Risk factor analyses gave relative risks for survival and suitability for definitive surgery. These analyses found that the more complex the lesion, the worse the outcome, particularly for those with systemic outflow obstruction. Based on these past patients, the methodology uniquely enabled the estimation of future survival and/or suitability for definitive repair, as determined by a new individual patient's morphological and physiological sub-group at presentation. Patients with aortic arch obstruction inevitably developed subaortic stenosis after conventional palliation, justifying the use of higher risk primary palliation, whilst isolated banding of the pulmonary trunk provided good palliation for those with the same morphological substrate without an arch lesion. The

results and extensive literature review support undertaking definitive surgery during early childhood, to balance the risks of young age against the development of adverse risk factors to a successful repair. Conclusions and recommendations for the future management of these children are made.

To my wife Michèle, to my parents Frances and Joe Franklin and to my uncle Owen Franklin, whose love and support over the years have made this study possible.

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The heart is the sun; and as the sun acts upon the earth and upon itself, so also acts the heart upon the body and upon itself.

Paracelsus (1493-1541)

Chapter 1

Introduction and aims of the study

1.1 Patients with a univentricular atrioventricular connection

Patients with a univentricular atrioventricular connection have complex congenital heart disease that is characterised by the fact that they have *functionally* only one ventricle. In contrast to the normal heart, in which each atrium is connected to its own ventricle (biventricular atrioventricular connections), in these hearts the atriums connect, for the most part, to only one ventricle. The ventricle therefore receives and combines the blood from both the systemic and pulmonary venous circulations. Hearts with a univentricular atrioventricular connection divide into three main morphological sub-groups: tricuspid atresia, double inlet ventricle and mitral atresia (see Chapter 2 and Figure 2.3, page 43). This retrospective study examines only patients with tricuspid atresia and double inlet ventricle. Patients with mitral atresia were excluded because of the difficulty in differentiating patients with true mitral atresia from those patients assumed to have the hypoplastic left heart syndrome using historical data (see

Chapter 7, page 173). Although children with tricuspid atresia and double inlet ventricle comprise only 2.5-5% of children with congenital heart defects or approximately 2-4 per 10,000 live births (Hoffman, 1990; Rao, 1992b), such patients represent 5-10% of term neonatal hospital admissions for congenital heart disease (Moller et al, 1995). Moreover, they are at the cutting edge of paediatric cardiology practice and have received much attention over recent years for several reasons.

Firstly, the very complexity of the pathology has meant that there continues to be controversy concerning the morphological classification and terminology of these hearts, particularly those with double inlet ventricle. This has resulted in confusion and ambiguity in the literature (see Chapter 2, page 58). Consequently, it has been difficult to compare the reports from different institutions and to comprehend the full morphological spectrum of these lesions in the clinical context. An insight into the true natural history of these patients and their surgically modified outcomes remains a significant gap in the understanding of these lesions.

Secondly, relatively recent advances in child health screening and diagnostic techniques, particularly cross sectional echocardiography, have meant that most patients now have a complete diagnosis made during infancy. Thus, it has only been possible in the last two decades to examine a true full cohort of these patients with complex congenital heart disease as they have presented during infancy.

Thirdly, although a few patients may survive into early adulthood either without surgical intervention because of 'naturally balanced' physiology (Dick et al, 1975;

Williams et al, 1976; Moodie et al, 1984b), or using palliative surgical means to augment or decrease pulmonary blood flow (Dick et al, 1975; Williams et al, 1976; De Brux et al, 1983; Moodie et al, 1984b; Stefanelli et al, 1984; Franklin et al, 1991b); the long term results of such strategies are not encouraging (Taussig at al, 1973; Dick et al, 1975; Williams et al, 1976; Trusler and Williams, 1980; De Brux et al, 1983; Moodie et al, 1984a, 1984b; Stefanelli et al, 1984; Franklin et al, 1991a, 1991b, 1993). However, surgical advances now enable such patients to undergo separation of their pulmonary and systemic circulations, either by the Fontan operation and its later modifications (Fontan and Baudet, 1971; Mayer et al, 1986) or, for patients with double inlet ventricle, by a dominant ventricular septation procedure (Ionescu et al, 1973; Pacifico, 1986). These have lead to improved survival and quality of life, at least in the short to medium term (Kirklin et al, 1986; Humes et al, 1987; Zwellers et al, 1989; Fontan et al, 1990; Gewillig et al, 1990a, 1990b; Mair et al, 1990; Nakazawa et al, 1990), and to the hope that most patients can be offered such 'definitive' surgery. This goal of therapy requires that the individual patient must not only survive until childhood in order to undergo such definitive palliation, but must also have suitable anatomy and haemodynamics for the operation to be successful (Choussat et al, 1978; Bargeron, 1987). This in turn, engenders difficult management decisions which need to be made soon after the diagnosis has been established, as most patients will require the judicious use of palliative surgery in infancy to ensure such suitability.

The influences of different medical and palliative operation strategies undertaken in infancy on survival and subsequent suitability for definitive repair are crucial, but have not been studied in an unselected population in the Fontan era (Franklin et al, 1991c).

Previous reports have either described the outcome of patients who were managed during an era when the Fontan operation was not widely performed (Campbell, 1961; Dick et al, 1975; Williams et al, 1976; Patel et al, 1978); have reported only older children whose outcome was inevitably influenced by factors favouring survival (Moodie et al, 1984a, 1984b; Stefanelli et al, 1984); or have only given the results of highly selected surgical series, usually definitive surgery alone (Kawashima et al, 1976; McGoon et al, 1977; Gale et al, 1979; Trusler et al, 1980; Feldt et al, 1981; De Brux et al, 1983; Cleveland et al, 1984; Kurosawa et al, 1990; Mair et al, 1990; Cohen et al, 1991; Mayer et al, 1992; Pearl et al, 1992; Weber et al, 1992). Yet others have only investigated a specific morphologic subset of patients (Stein et al, 1990; Culbertson et al, 1992) or have described a cohort of patients without examining the relationship of morphology and management strategies on outcome (Fesslova et al, 1989; Tam et al, 1989).

This retrospective study therefore reports an unselected, consecutive series of 191 patients with double inlet ventricle and 237 patients with tricuspid atresia, who presented to two tertiary institutions during the Fontan era at less than one year of age over a 15 year period. The aims were:

1. To report in detail the full morphological spectrum of the two patient groups in the light of present day diagnostic techniques and terminology.

2. To study the 'natural history' of the two groups prior to definitive surgery by determining, using risk factor analyses, the morphological and physiological factors

which influenced presentation and survival. In so doing, methods to predict the outcome of future infants with different variants of double inlet ventricle and tricuspid atresia would be established, based on the past experiences of the patients examined in this series.

3. To examine the ability of palliative surgery to improve the natural history of the patients with double inlet ventricle after their initial presentation to the tertiary centres. This would use sophisticated statistical techniques to compare the outcome of those patients undergoing palliation with those not undergoing such surgery, whilst taking into account their underlying morphology and haemodynamics.

4. To establish the proportions and characteristics of the two patient groups at initial presentation to the tertiary centres in infancy in terms of whether they were, or were not, potential candidates for future definitive surgery by either a Fontan-type operation or a ventricular septation procedure.

5. To evaluate the effectiveness of medical and surgical management during infancy and childhood in achieving both survival and subsequent suitability for an eventual Fontan-type operation or ventricular septation procedure (in double inlet ventricle patients). These results would then be used to infer an optimum age range at which definitive surgery might be undertaken.

6. To examine the special problem of subaortic stenosis in these patients (see below).

These data should provide the clinician with a comprehensive and relevant framework upon which to base decision making and thus optimise therapy for individual infants with these complex malformations.

1.2 The development of subaortic stenosis

Subaortic stenosis in patients with double inlet ventricle or tricuspid atresia occurs almost exclusively in cases with a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow (Figure 1.1). In such patients, blood for the systemic circulation must exit the dominant left ventricle via a ventricular septal defect to enter the rudimentary right ventricle, before reaching the aorta. The ventricular septal defect is usually entirely muscle bound and thus potentially restrictive (Anderson et al, 1985; Rao, 1992d). Furthermore, many of these patients will have additional coarctation or interruption of the aortic arch. In order to ensure the low pulmonary arteriolar resistance necessary for a later successful Fontan-type procedure (Choussat et al, 1978; Kirklin et al, 1986), pulmonary blood flow must be restricted in early infancy (Juaneda and Haworth, 1984, 1985). The conventional approach to achieve this has been to band the pulmonary trunk and repair any associated aortic arch lesion. However, banding of the pulmonary trunk may promote ventricular hypertrophy (Kirklin et al, 1986; Seliem et al, 1989; Cohen et al, 1991) and this will accelerate the natural tendency of the ventricular septal defect to close, producing subaortic stenosis (Mesko et al, 1973; Freedom et al, 1986; Rao, 1992d).

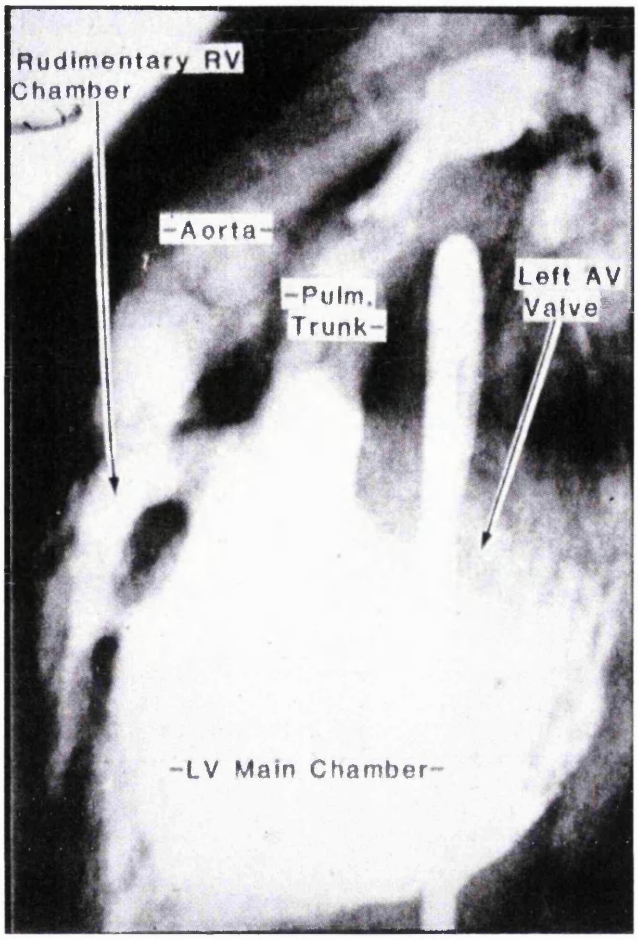

Figure 1.1. Angiographic frame illustrating the morphology of patients with the propensity for developing subaortic stenosis: a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow. In this patient with tricuspid atresia, there are two relatively restrictive ventricular septal defects between the left ventricle and the markedly hypoplastic right ventricle.

AV, atrioventricular; LV, left ventricle; Pulm., pulmonary; RV, right ventricle.

As subaortic stenosis and ventricular hypertrophy are both adverse incremental risk factors for a successful Fontan-type operation or ventricular septation procedure (Kirklin et al, 1986; Pacifico, 1986; Cohen et al, 1991), some centres have concluded that banding of the pulmonary trunk is an inappropriate therapy for virtually all patients

with this anatomy (Freedom, 1987; Rothman et al, 1987). Early palliation with higher risk procedures, such as a Norwood-type approach (disconnecting the pulmonary trunk for use in reconstructing the systemic outflow tract and construction of a systemic-to-pulmonary arterial shunt; Norwood et al, 1983; Rychik et al, 1991), has been advocated (Freedom, 1987; Rothman et al, 1987). However, conclusive data supporting this approach are lacking.

A separate study was therefore undertaken of the sub-population of 102 consecutive infants with the above morphological substrate prone to the development of subaortic stenosis. The aim was to determine the influence of banding of the pulmonary trunk on the development of subaortic stenosis and to identify patients at particularly high risk of this complication. This would enable a sounder basis for the selection of the different palliative approaches described above, in this difficult group of infants.

Hearts have as many fashions as the world has shapes.

Ovid (43 BC - ? 17 AD)

Chapter 2

Morphology - definitions and nomenclature [1]

Historically there has been considerable disagreement between paediatric cardiac morphologists when describing hearts with tricuspid atresia and double inlet ventricle. To aid understanding, the terminological methods, nomenclature and definitions used in this thesis are initially detailed, before separately putting them into an historical perspective. Throughout this study the sequential segmental approach with the terminology of Anderson and colleagues has been used (1983, 1984, 1987c; Elliott et al, 1989; Anderson, 1996).

2.1 The segmental sequential approach

Over the last 20-30 years paediatric cardiac morphologists have been especially concerned with the development of a comprehensive, unambiguous and user friendly system of classification for congenital heart lesions. It is now almost universally

[1] All figures in Chapter 2 and Figure 11.1 were provided by Professor R H Anderson and reproduced with kind permission.

accepted that the segmental sequential approach, as proposed by Van Praagh in 1972, is the most viable. It is dependent only on observed and observable anatomic data, whilst ignoring speculative embryological and morphogenetic considerations. This approach simply involves systematically describing, in mutually exclusive terms, all chamber and vessel morphologies, connections and relations. Although there is general agreement about using this structured approach, there remains internationally a variable degree of controversy as to which terms are best suited to describe the atriums, some chamber relationships and their interconnections (see below). Currently, the approach and terms proposed and summarised by Anderson and co-authors (1987a; Anderson, 1996), have been adopted by most centres, particularly in Europe, as well as in the present study.

In practical terms, the description of any heart first involves the recognition of the three segments of the heart with their various components: the atriums (right and left), the ventricles (right, left and indeterminate) and the arterial trunks (pulmonary, aortic, common and solitary). Each component has clearly defined characteristics which distinguish it from the other components within the particular segment (Table 2-1). Thus, the atrial chambers are distinguished by the differing morphology of their appendages and internal musculature. The right atrium has a broad appendage with pectinate muscles extending bilaterally around the atrioventricular junction to the crux, whilst the left atrium has a hook or tube-like appendage with pectinate muscles confined to the appendage area, there being a smooth vestibule. A ventricle may be defined as having inlet, outlet and apical trabecular components, but it is only the trabecular component which is consistently present and which has constant features useful for differentiating the different ventricular morphologies. Thus, the right ventricle has

coarse apical trabeculations, in contrast to the fine ones of the morphological left ventricle. These two patterns are relatively distinct from the very coarse trabeculations found in the ventricle with an indeterminate morphology, which is already distinguishable by being a solitary chamber. The great arterial trunks are then clearly identified by their different branching patterns (Table 2-1).

Once the above components of each segment have been identified, their interrelationships within the heart can be systematically detailed. Firstly, the atrial arrangement (situs) is specified and described. This is followed by delineation of the type and mode of connections between the atrial and ventricular chambers, and the type and mode of connections between the ventricular chambers and great arteries (Table 2-1). The *type* of atrioventricular or ventriculo-arterial connection refers to the morphology of the communication between these respective chambers and the great arteries.

This is distinct from the *mode* of the atrioventricular or ventriculo-arterial connection, which describes the morphology of the valves themselves and the way that they connect and relate to the ventricular mass (Table 2-1). Between the atrial and ventricular chambers, there may be two atrioventricular valves, a common atrioventricular valve with a common atrioventricular orifice or one of two atrioventricular valves may be so poorly formed that the respective atrioventricular junction is unguarded. Any of these valves may straddle and/or override the ventricular septum and the individual valve may be perforate or imperforate (Figure 2.1). Evidently both of two atrioventricular valves cannot be imperforate and only one part or component of a common

atrioventricular valve may be imperforate. The possibilities for the mode of ventriculo-arterial connection are similar in that one of two valves (i.e., the aortic or pulmonary valve) may be perforate or imperforate, whilst a common or solitary valve will always be patent. In addition any valve may override the ventricular septum to a varying degree.

The spatial relationships between the chambers and vessels are next described along with any abnormal features, before detailing any additional anomalies that may be present, such as septal defects, valve lesions and/or anomalous venous connections. Finally, an account of any acquired lesions is given, such as surgical modifications to the anatomy.

Table 2-1. Diagnostic steps in segmental sequential analysis of congenital heart lesions - I

Sequential step	Description
Chamber recognition	
Right atrium	broad appendage, pectinate muscles extending bilaterally around AV junctions to crux
Left atrium	hook/tube like appendage, pectinate muscles only therein, smooth vestibule
Right ventricle	ventricular chamber with coarse apical trabeculations
Left ventricle	ventricular chamber with fine apical trabeculations
Indeterminate ventricle	single, solitary ventricular chamber with very coarse trabeculations
Atrial arrangement (situs)	
Usual (solitus)	right atrium to right of left atrium
Mirror image (inversus)	right atrium to left of right atrium
Right atrial isomerism	bilateral right atriums
Left atrial isomerism	bilateral left atriums
Types of atrioventricular connection(s)	
Biventricular atrioventricular connections	
Concordant	right atrium connected to right ventricle, left atrium connected to left ventricle
Discordant	right atrium connected to left ventricle, left atrium connected to right ventricle
Ambiguous	Each atrium in bilateral left or right atriums connected to separate ventricles
Univentricular atrioventricular connection	
Double inlet	both atriums connect to a single dominant ventricle (RV, LV or IV)
Absent right ("tricuspid atresia")	only the left sided atrium connects to a single dominant ventricle (RV, LV or IV)
Absent left ("mitral atresia")	only the right sided atrium connects to a single dominant ventricle (RV, LV, or IV)
Uniatrial biventricular connection	
Absent right with straddling AV valve	left sided atrium connected to both right and left ventricular chambers
Absent left with straddling AV valve	right sided atrium connected to both right and left ventricular chambers

Table 2-1. Diagnostic steps in segmental sequential analysis of congenital heart lesions - II

Sequential step	Description
Types of ventriculo-arterial connection(s)	
Concordant	pulmonary trunk from right ventricle, aorta from left ventricle
Discordant	aorta from right ventricle, pulmonary trunk from left ventricle
Double outlet	both aorta and pulmonary trunk arising from the same ventricle (RV, LV or IV)
Single outlet	only a single outlet from the heart: pulmonary trunk, aorta, a common arterial trunk or a solitary arterial trunk (distinguished by having absent intrapericardial pulmonary arteries). The single outlet may arise from a single ventricle (RV, LV or IV) or may straddle both ventricles.
Mode of atrioventricular connection	
Two atrioventricular valves	mitral or tricuspid valve; in complex hearts, may be better termed left or right atrioventricular valve either may be perforate or imperforate either may straddle and/or override the ventricular septum
Common atrioventricular valve	usually has five leaflets; part of atrioventricular septal defect anomaly may be partially or completely tethered to ventricular septum, or free floating may straddle and/or override the ventricular septum one component may be imperforate
Unguarded atrioventricular orifice	complete absence of mitral or tricuspid valve, leaving 'gaping' connection
Mode of ventriculo-arterial connection	
Two ventriculo-arterial valves	either may be perforate or imperforate either or both may or override the ventricular septum
Common valve	as in a common arterial trunk - may override the ventricular septum
Solitary valve	as in a solitary arterial trunk - may override the ventricular septum

Table 2-1. Diagnostic steps in segmental sequential analysis of congenital heart lesions - III

Sequential step	Description
Spatial relationships of the heart in the thorax and the chambers and vessels to each other:	
right / left, anterior / posterior / side-by-side, superior / inferior	
Associated lesions - not a comprehensive listing	
Anomalies of the systemic veins	left or bilateral superior caval vein(s) azygos continuation of inferior caval vein
Anomalies of the pulmonary veins	partially or totally anomalous connections individual or multiple vein stenosis(es) or atresia
Anomalies of the atrium(s)	cor triatriatum, supravalvar fibrous shelf
Anomalies of the interatrial septum	atrial septal defect(s), common atrium
Anomalies of the atrioventricular valves	stenosis, hypoplasia, regurgitation, Ebstein's anomaly, leaflet abnormalities
Anomalies of the ventricle(s)	hypoplastic, rudimentary chamber; outflow tract obstruction at various levels
Anomalies of the interventricular septum	ventricular septal defect(s)
Anomalies of ventriculo-arterial valves	stenosis, hypoplasia, regurgitation, leaflet anomalies
Anomalies of great arteries	hypoplasia, stenosis / coarctation, interruption
Anomalies of other systemic arteries	patent arterial duct; aberrant vessels; vascular rings coronary artery anomalies and fistulae systemic to pulmonary artery collateral arteries
Miscellaneous anomalies	arteriovenous fistulae, conduction tissue abnormalities
Acquired heart disease - examples	
Cardiomyopathies, valve lesions, endocarditis, coronary artery disease, Kawasaki's disease, rheumatic fever	
Surgical / transcatheter procedures:	closures, modifications, constructions, interpositions, ligations, redirections and/or implantations

AV, atrioventricular; IV, ventricle of indeterminate morphology; LV, morphological left ventricle; RV, morphological right ventricle; VA, ventriculo-arterial.

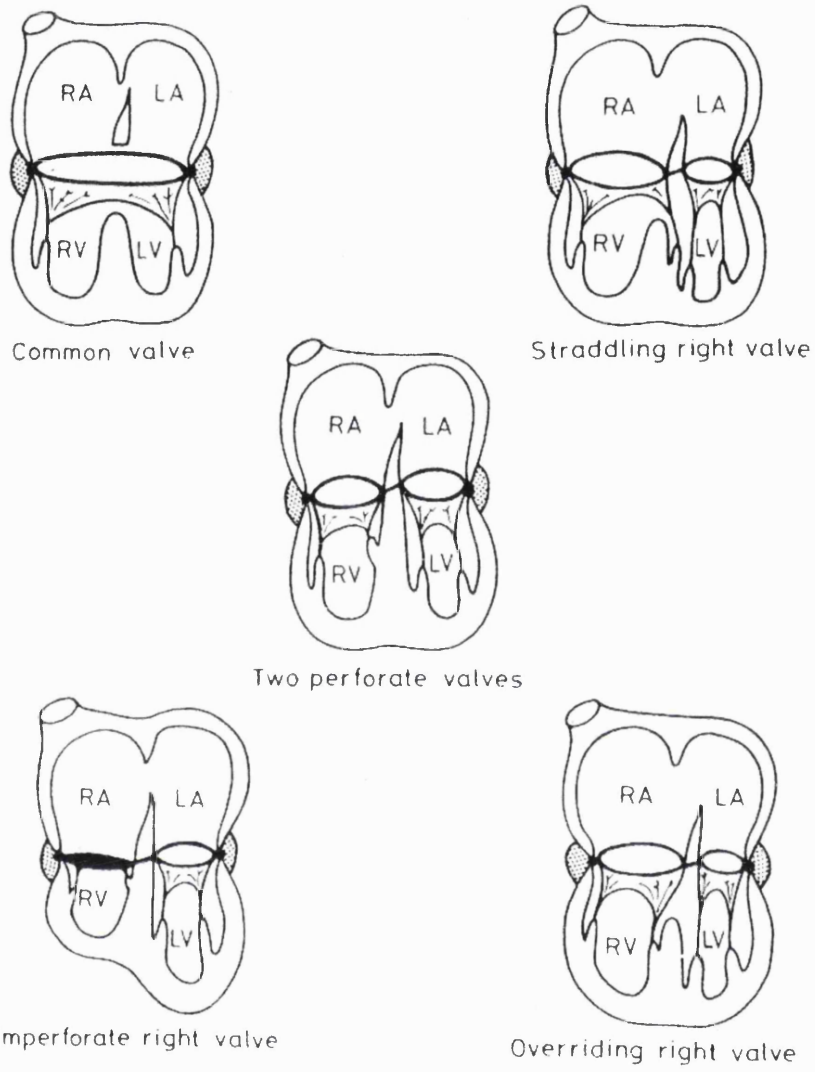

Figure 2.1. Diagrams of the different modes of atrioventricular connection that can exist when both atrial chambers have a connection to the ventricular mass. Alternatively, it could be the *left* atrioventricular valve that is straddling, overriding or imperforate.
LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

2.2 The univentricular atrioventricular connection

The normal heart is characterised as having *biventricular* atrioventricular connections, such that each atrium is connected to its own ventricle in a concordant arrangement, either with the usual atrial arrangement (situs solitus) or its mirror image (situs inversus) (Figure 2.2); i.e., the morphological right atrium connects to the morphological right ventricle and the morphological left atrium connects to the morphological left ventricle.

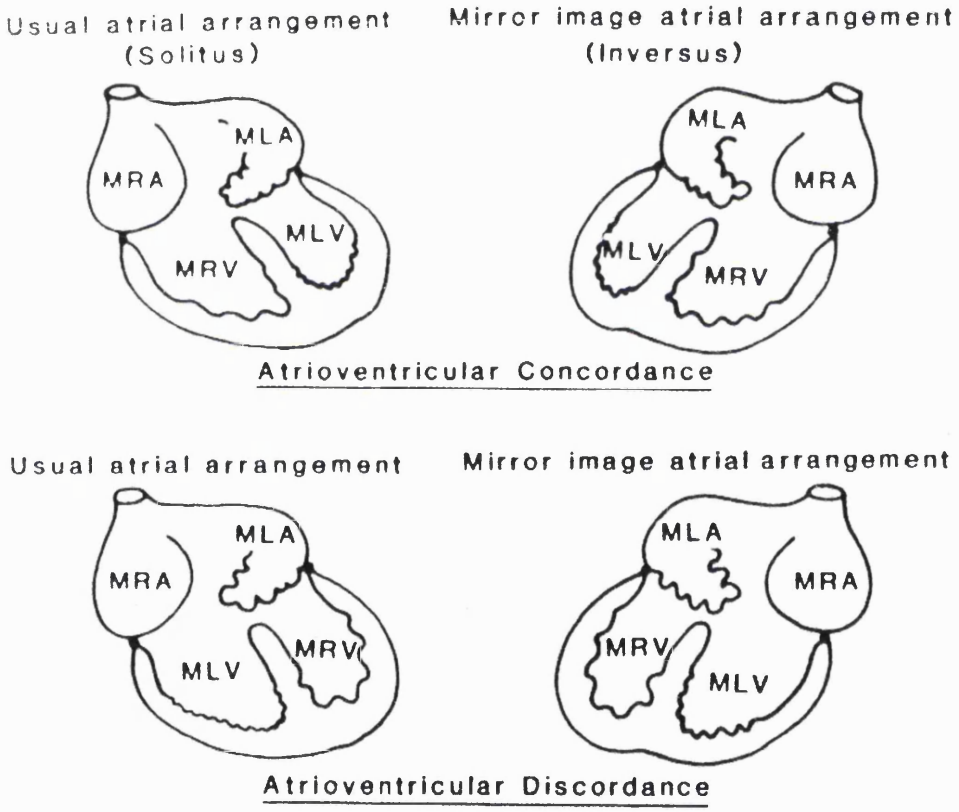

Figure 2.2. Diagrams illustrating that only two atrioventricular connections, concordant and discordant, are possible when the atrial chambers are lateralised with either the usual or mirror image arrangement and each atrium is connected to only one ventricle.
MLA, morphological left atrium; MRA, morphological right atrium; MLV, morphological left ventricle; MRV, morphological right ventricle.

Congenital heart lesions will usually be associated with concordant biventricular atrioventricular connections. Much less commonly, the biventricular connections may be discordant (Figure 2.1) or ambiguous, in the setting of bilateral right or left atriums (right or left isomerism of the atrial appendages), as 'half' of such hearts will have a concordant atrioventricular connection and the other 'half' a discordant connection (see below).

Hearts with a *univentricular* atrioventricular connection are simply defined as those in which both atriums connect dominantly to only one ventricular chamber. They are subdivided according to the *type* of atrioventricular connection (Figure 2.3): either both atriums connect directly to the dominant ventricle, termed 'double inlet ventricle' (Figure 2.4); or only one atrium communicates directly to the ventricular mass, due to the absence of either the right or left atrioventricular valve, so called 'tricuspid' or 'mitral atresia'. In the latter case, the atrium associated with the absent atrioventricular valve of necessity connects indirectly to the ventricular mass via an interatrial communication, such as an atrial septal defect. The univentricular atrioventricular connection may coexist with any atrial arrangement (Figures 2.3 and 2.5): usual (solitus), mirror-image (inversus) or ambiguous (right or left isomerism of the atrial appendages; also known as right or left atrial isomerism). Right atrial isomerism is particularly associated with anomalies of the pulmonary venous connections and asplenia. Left atrial isomerism usually coexists with an interrupted inferior caval vein with azygous continuation of its course superiorly to join a left or right superior caval vein which then connects to the heart, as well as polysplenia (Uemura et al, 1995a, 1995b).

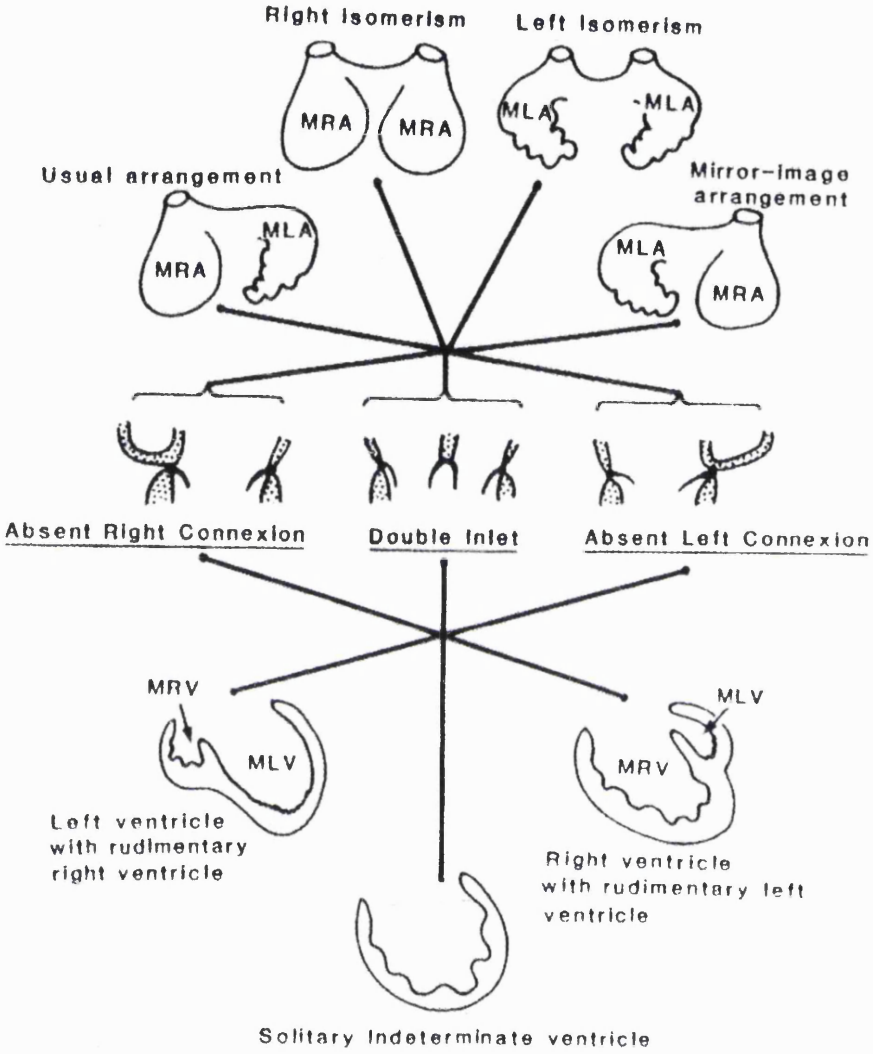

Figure 2.3. Diagram demonstrating that any of the three *types* of a univentricular atrioventricular connection (double inlet, absent right and absent left) can co-exist with any atrial arrangement and that this connection may be dominantly to any one of the three ventricular morphologies. Note that there is marked variability in the spatial relationships between the left and right ventricles, and that these are simplified here for clarity.

MLA, morphological left atrium; MRA, morphological right atrium; MLV, morphological left ventricle; MRV, morphological right ventricle.

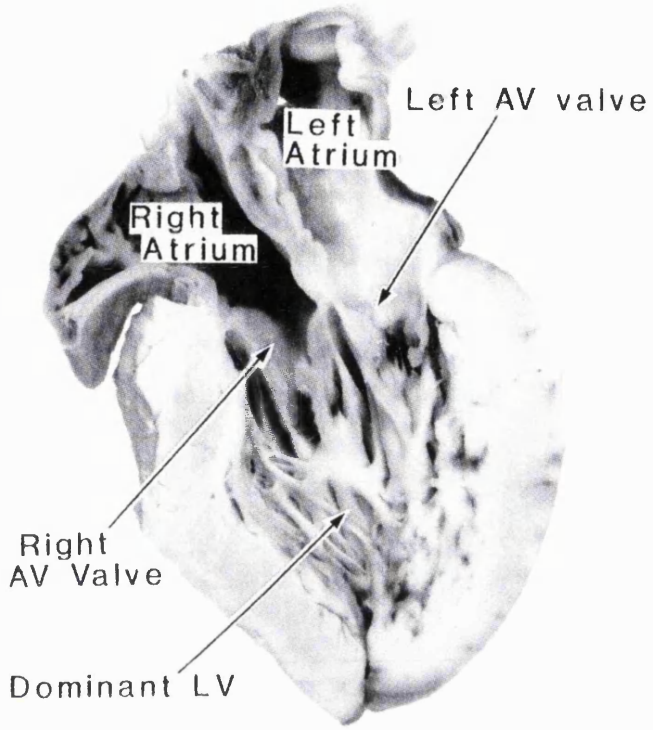

Figure 2.4. Heart sectioned in a four chamber plane to illustrate the essence of double inlet ventricle. Both atriums and atrioventricular valves are connected dominantly to the same ventricle; in this case, with left ventricular morphology.

AV, atrioventricular; LV, left ventricle.

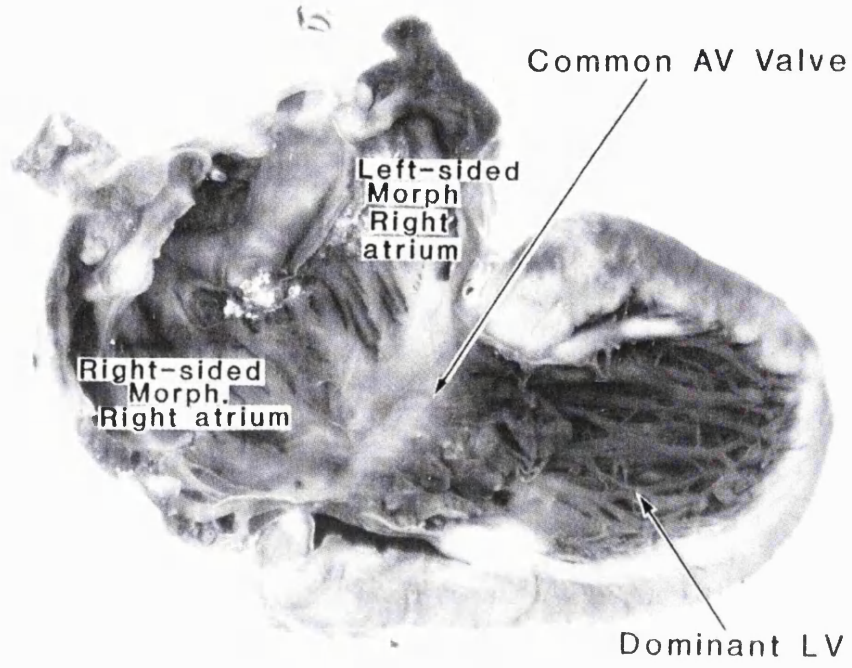

Figure 2.5. Heart sectioned in a four chamber view showing that the atrioventricular junction may alternatively be guarded by a common atrioventricular valve in double inlet ventricle, in this case with a dominant left ventricle. Both atriums, here with right atrial isomerism, connect to the one ventricle.
AV, atrioventricular; LV, left ventricle; Morph, morphological.

Any variant of the *mode* of atrioventricular connection may occur. In double inlet ventricle, the mode of atrioventricular connection to the dominant ventricle may either be by two atrioventricular valves (Figures 2.4 and 2.6), or by a common atrioventricular valve (Figure 2.5). In addition, any of these valves may override the ventricular septum with or without straddling of the tension apparatus (Figure 2.7). To accommodate this fact, double inlet ventricle is further defined as when there is a commitment of more than 50% of each of two atrioventricular valves or more than 75% of a common valve orifice to the same ventricle (Kirklin et al, 1973), as illustrated in Figure 2.8. In other words, although there is a shift in ventricular dominance with increasing degrees of commitment to the right or left ventricle, it is not until over 50% of the right or left

atrioventricular valve, or over 75% of a common atrioventricular valve is so committed, that the type of atrioventricular connection changes from being classified as biventricular to one that is univentricular.

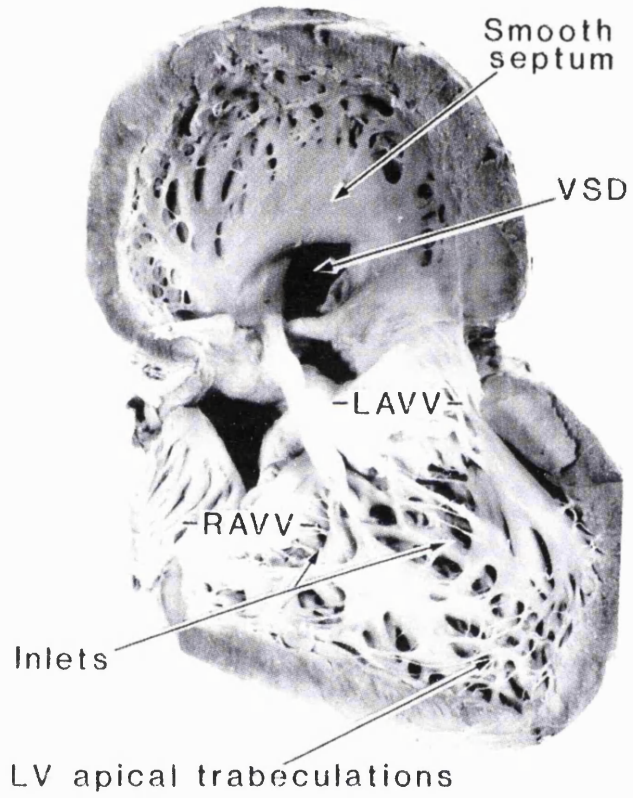

Figure 2.6. Clam shell section of a heart with double inlet left ventricle via two atrioventricular valves and discordant ventriculo-arterial connections, the most common arrangement found in patients with double inlet left ventricle. A non-restrictive ventricular septal defect is also well shown. Note the fine apical trabeculations which confirm this to be a morphological left ventricle.

LAVV, left atrioventricular valve; LV, left ventricular; RAVV, right atrioventricular valve; VSD, ventricular septal defect.

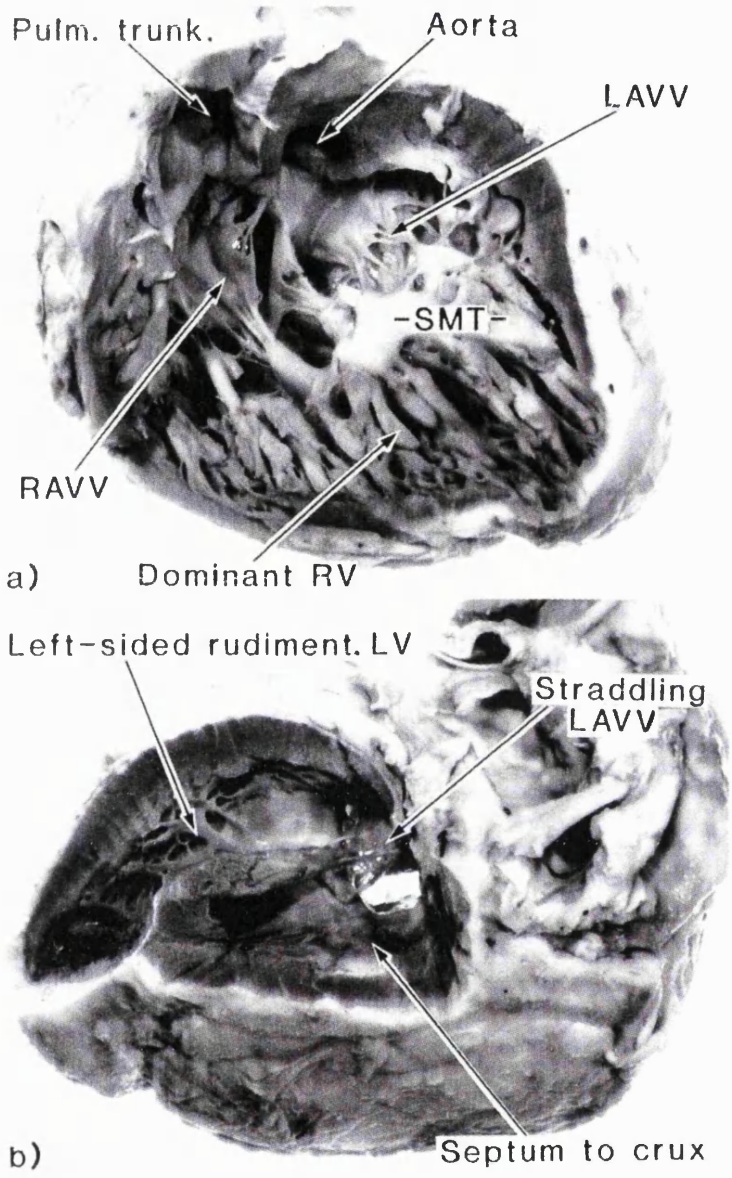

Figure 2.7. Sections of a heart with double inlet right ventricle via two atrioventricular valves, the left one straddling the ventricular septum from the single papillary muscle in the rudimentary left sided, posterior left ventricle. The aorta and pulmonary trunk both arise from the dominant right ventricle such that the type of ventriculo-arterial connection is double outlet from the right ventricle.

LAVV, left atrioventricular valve; LV, left ventricle; pulm., pulmonary; RAVV, right atrioventricular valve; rudiment., rudimentary; RV, right ventricle; SMT, septomarginal trabeculation.

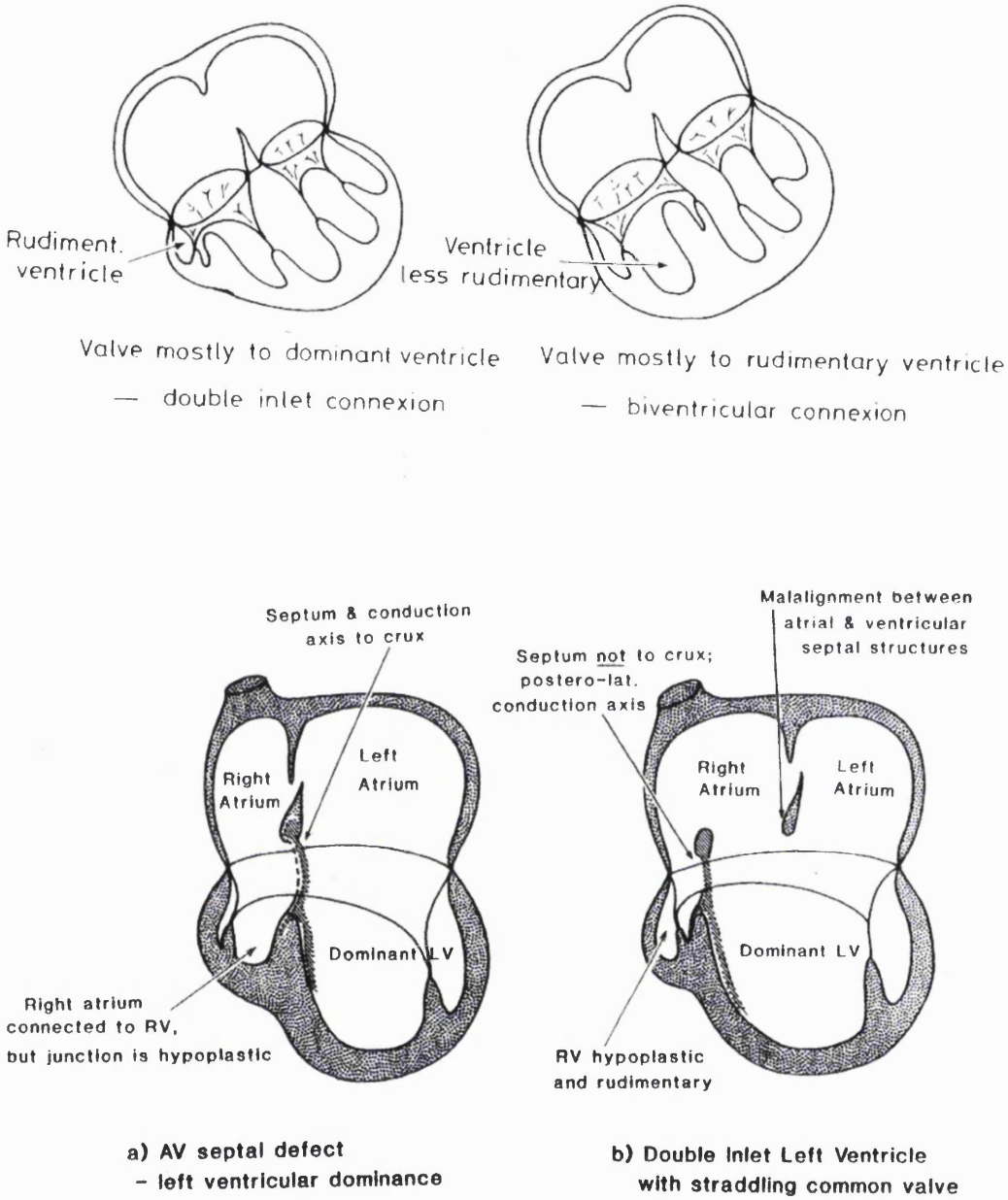

Figure 2.8. Diagrams to demonstrate the way the degree of commitment of an overriding and straddling atrioventricular valve determines the *type* of atrioventricular connection. The upper panel shows that in the setting of two atrioventricular valves, the cross over is when the commitment is more than 50% to the dominant left ventricle, whilst in the lower panel it depends upon a greater than 75% commitment of a common atrioventricular valve. Additionally in the lower panel, there is marked malalignment of the atrial and ventricular septae, a fact which also distinguishes concordant atrioventricular connections with left ventricular dominance **(a)**, from double inlet left ventricle **(b)**.

AV, atrioventricular; LV, left ventricle; postero-lat., postero-lateral; Rudiment., rudimentary; RV, right ventricle.

Finally, one of the two atrioventricular valves may be imperforate so that the only barrier between the atrium and the ventricular mass is the atrioventricular valve tissue itself. In this situation, the underlying *type* of atrioventricular connection persists, whether it be part of a biventricular (concordant, discordant or ambiguous) connection or part of a double inlet univentricular atrioventricular connection (Figure 2.9).

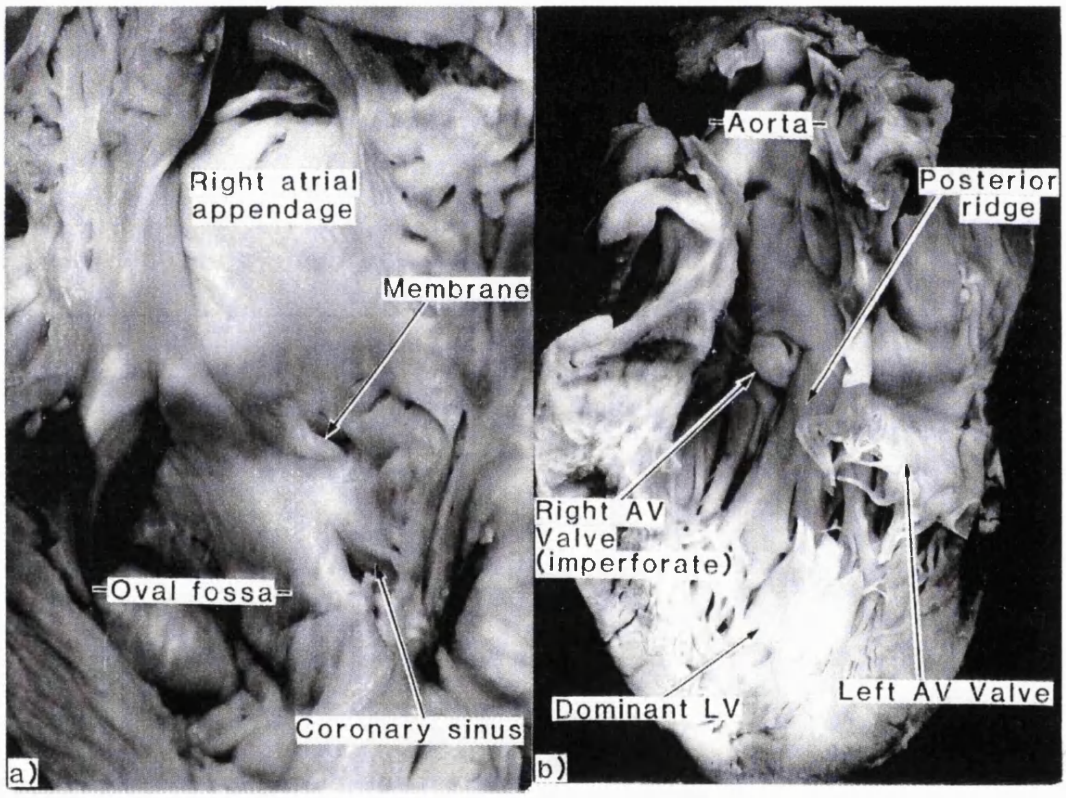

Figure 2.9. Sections of a heart with double inlet left ventricle via two atrioventricular valves, the right one of which is imperforate, as if with a 'membrane' across its orifice. Panel **a)** shows the right atrial aspect and **b)** as viewed from the dominant left ventricle. Haemodynamically this heart functioned as one with 'tricuspid atresia', with a widely patent interatrial oval fossa.

AV, atrioventricular; LV, left ventricle.

In contrast, when an atrioventricular connection is absent (as in tricuspid or mitral atresia), the muscular floor of one of the atriums extends to the central fibrous body and is separated from the ventricular mass by the fibro-fatty tissue of the atrioventricular groove or sulcus, as in Figure 2.10. In this case, the sole atrioventricular valve will evidently be perforate but the valve may also override or straddle across the ventricular septum. In this latter scenario, a uniatrial biventricular connection is said to be present (Table 2-1; Anderson, 1996).

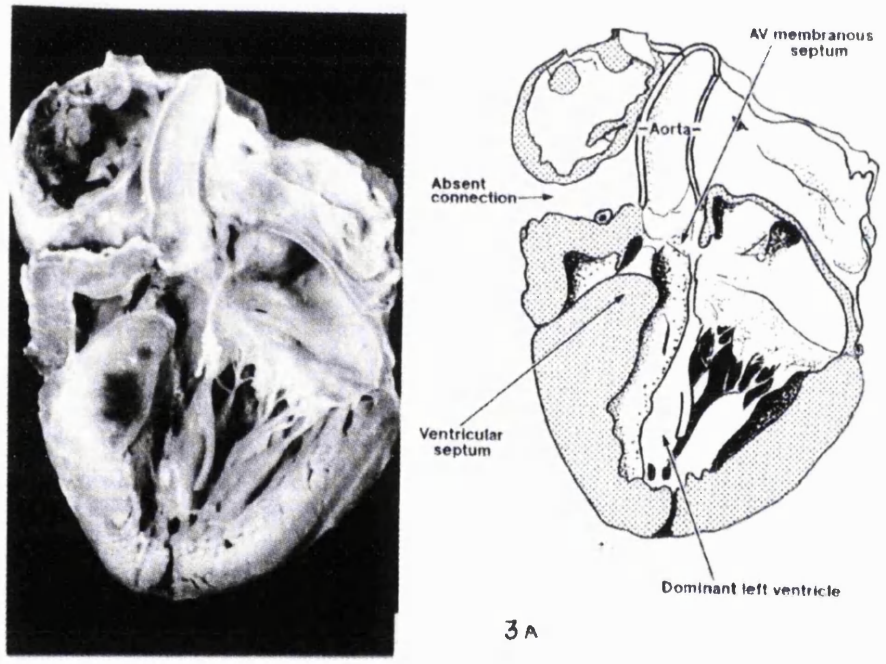

Figure 2.10. Heart with tricuspid atresia sectioned in the long-axis plane to show the absent right atrioventricular connection, with fibro-fatty tissue between the right atrium and rudimentary right ventricle.
AV, atrioventricular.

The univentricular atrioventricular connection may be to a dominant ventricle of left (Figures 2.4, 2.5, 2.6, 2.9 and 2.10) or right (Figure 2.7) morphology, or to a solitary ventricle of indeterminate morphology (Figure 2.11).

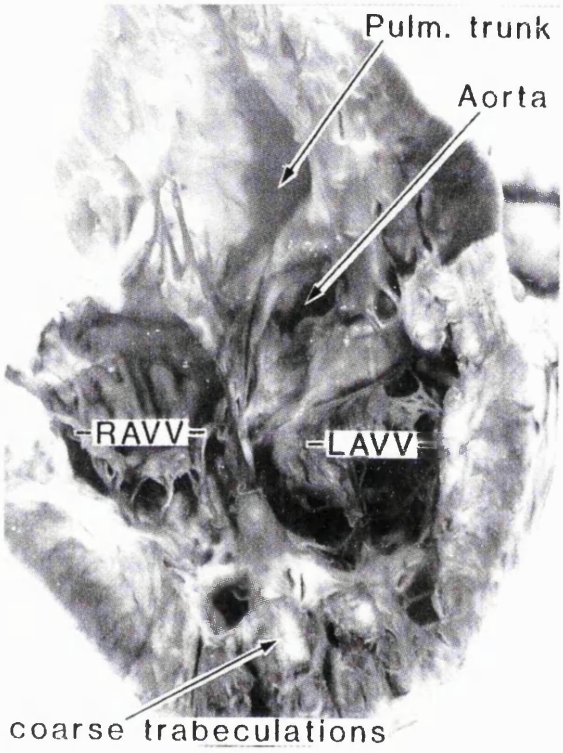

Figure 2.11. Heart sectioned to show double inlet via two atrioventricular valves into, and double outlet out of a solitary ventricle with indeterminate morphology.
LAVV, left atrioventricular valve; Pulm., pulmonary; RAVV, right atrioventricular valve.

In the case of a dominant left ventricle, there is a coexistent rudimentary right ventricle anterior to the atrioventricular valve(s) and anterior and superior to the left ventricle (Figures 2.10 and 2.12), whilst with a dominant right ventricle there is a rudimentary left ventricle posterior to the atrioventricular valve(s) and in a posterior and inferior position (Figure 2.7). The non-dominant chambers are termed 'incomplete', in that they

lack an inlet component. The outlet component of either ventricle may also be absent in the setting of a single outlet ventriculo-arterial connection (Table 2-1), whilst the apical trabecular portion of the rudimentary ventricle will always be present. In contrast, it is the lack of an associated second ventricle which is the major determining feature of a heart in which a sole ventricle is considered to have indeterminate morphology (Figure 2.11).

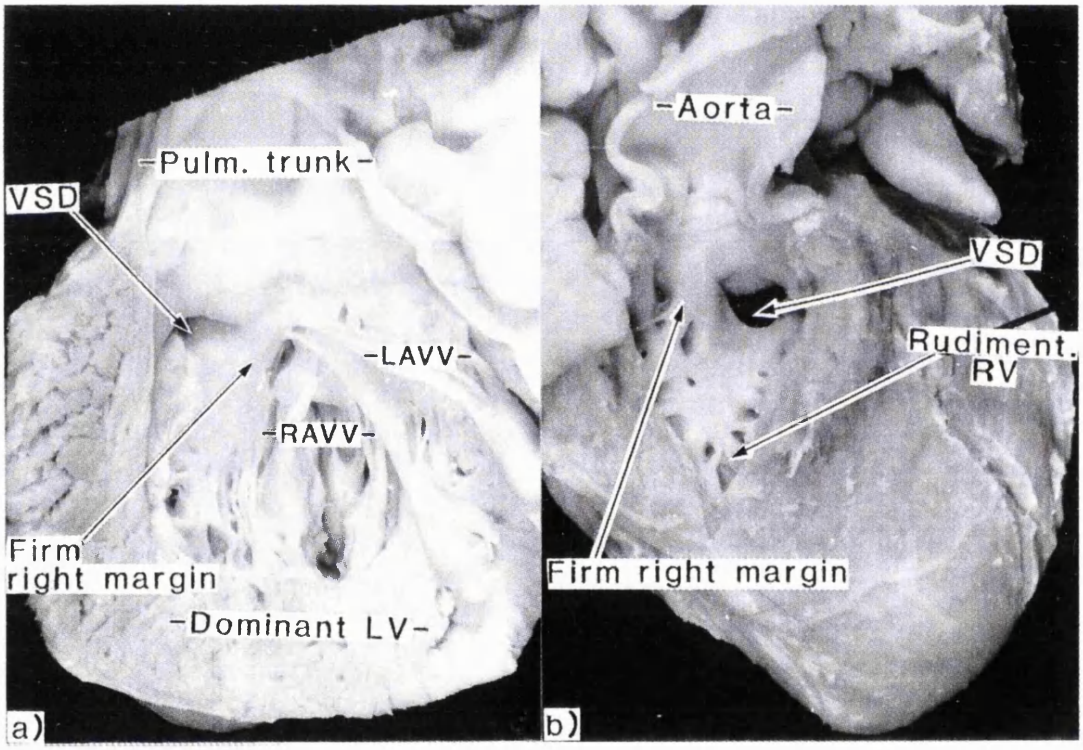

Figure 2.12.. Sections of a heart with double inlet left ventricle via two atrioventricular valves, to demonstrate the discordant ventriculo-arterial connections. The rudimentary right ventricle is anterior and right sided, and gives rise to the aorta.

LAVV, left atrioventricular valve; LV, left ventricle; Pulm., pulmonary; RAVV, right atrioventricular valve; Rudiment. RV, rudimentary right ventricle; VSD, ventricular septal defect.

Hearts with biventricular atrioventricular connections and a huge ventricular septal defect, sometimes called a 'common ventricle', have been excluded from the series, despite their common mixing physiology. They are characterised as having both right and left ventricular morphologies present in near equal proportions but with virtually no ventricular septum present.

Any type and mode of ventriculo-arterial connection may coexist with a univentricular atrioventricular connection (Table 2-1, Figure 2.13): concordant, discordant, double outlet from the dominant or rudimentary ventricle or single outlet from either ventricle (pulmonary atresia, aortic atresia, a common arterial trunk or a solitary arterial trunk). The most frequent type of ventriculo-arterial connection found in hearts with a double inlet atrioventricular connection is that of discordant connections (Figure 2.12), whilst the presence of concordant great arterial connections (the eponymous Holmes heart) is much less common (Figure 2.14; see Chapter 4, page 81). This is in contrast to hearts with an absent right atrioventricular connection in which concordant ventriculo-arterial connections are far more common (Figure 2.15; see Chapter 5, page 124).

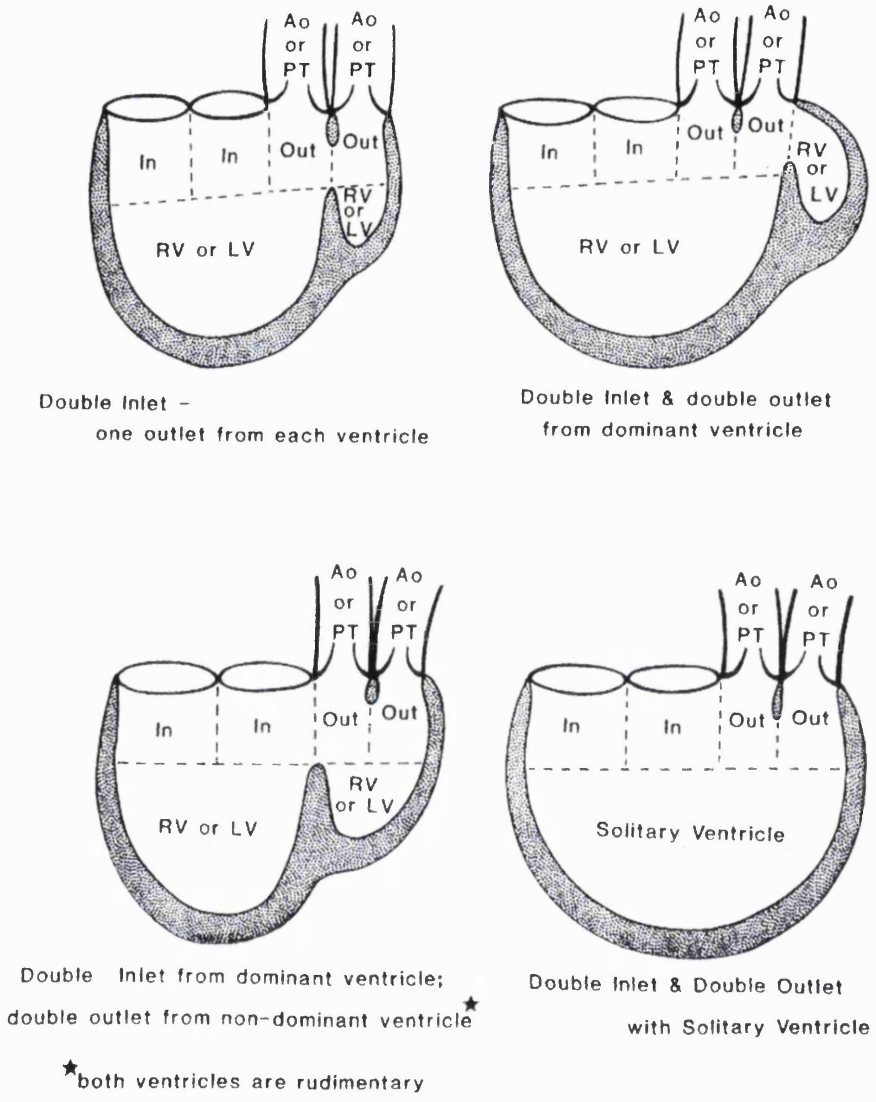

Figure 2.13. Diagrams to demonstrate that any type of ventriculo-arterial connection(s) is possible in hearts with a double inlet atrioventricular connection. The aorta or pulmonary trunk may arise from the left ventricle, the right ventricle or a solitary ventricle with indeterminate morphology; either alone or together with the other great artery. Equally, when there is only a single outlet present, the solitary great artery may also arise from any ventricle (not illustrated), as discussed in the text. The above also applies to hearts with an absent right or left atrioventricular connection (tricuspid or mitral atresia).

Ao, aorta; LV, left ventricle; PT, pulmonary trunk; RV, right ventricle.

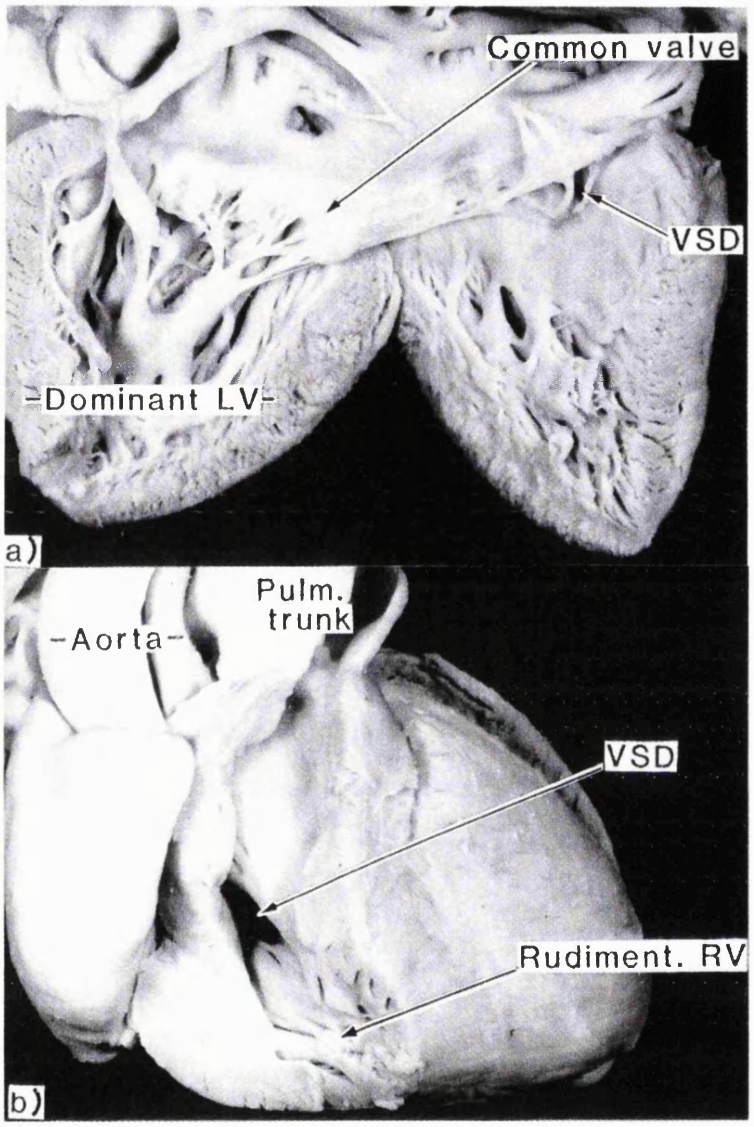

Figure 2.14. Sections from a heart with double inlet left ventricle and concordant ventriculo-arterial connections: an example of the 'Holmes heart' (1824). In this case there is a common atrioventricular valve and the ventricular septal defect is restrictive. The pulmonary trunk clearly arises from the rudimentary right ventricle.

LV, left ventricle; Pulm., pulmonary; Rudiment. RV, rudimentary right ventricle; VSD, ventricular septal defect.

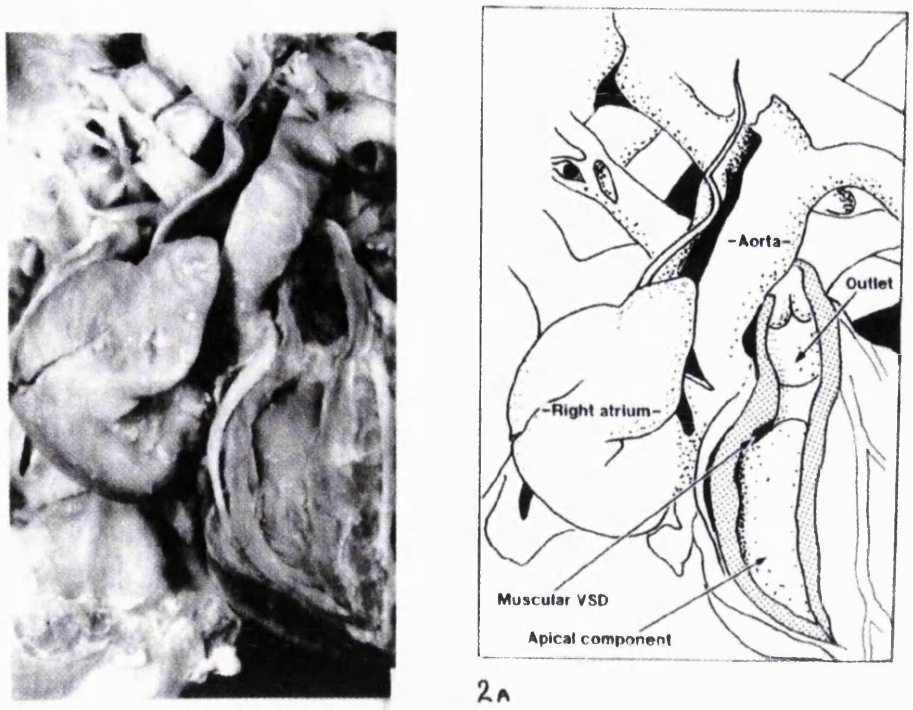

Figure 2.15. Section a from heart with tricuspid atresia and concordant ventriculo-arterial connections. The ventricular septal defect is markedly restrictive and there is also muscular narrowing above this defect, in the right ventricular outflow tract that leads up to the pulmonary trunk.

Outlet, pulmonary trunk; VSD, ventricular septal defect.

Most hearts with a univentricular atrioventricular connection and which have two ventricular chambers present, will have a ventricular septal defect between the two chambers. This may be restrictive, as is usually the case in those with tricuspid atresia and concordant ventriculo-arterial connections, leading to pulmonary outflow tract obstruction (Figure 2.15). Occasionally in this setting the ventricular septum is intact, effectively resulting in pulmonary atresia, even though the pulmonary valve itself is usually patent. If there is a dominant left ventricle and discordant ventriculo-arterial connections with a restrictive ventricular septal defect, subaortic stenosis results with

obstruction to the systemic outflow from the left ventricle (Figure 2.16). This is often associated with additional coarctation of the aorta or an interrupted aortic arch (see Chapter 6, page 156).

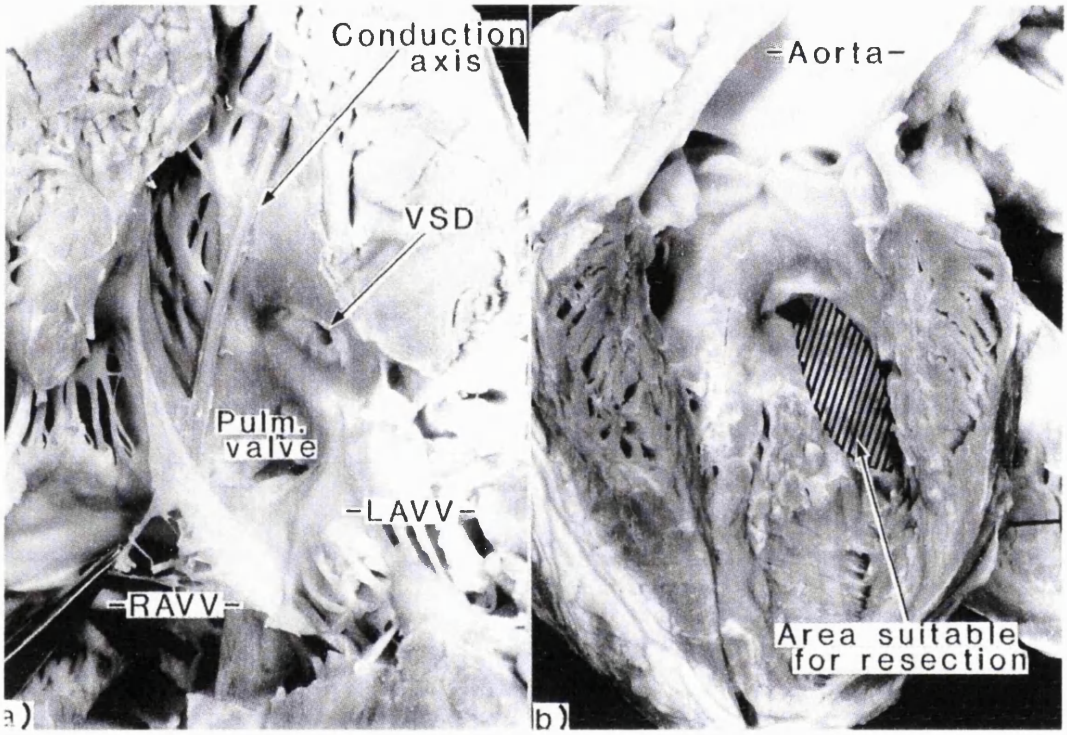

Figure 2.16. Sections through a heart with double inlet left ventricle via two atrioventricular valves and discordant ventriculo-arterial connections, to demonstrate a restrictive ventricular septal defect producing subaortic stenosis: **a)** shows the left ventricular aspect and **b)** shows the view from the left sided rudimentary right ventricle. The hatching represents the 'safe area' which can be resected to enlarge the ventricular septal defect and so relieve the obstruction, whilst avoiding the conduction tissue.
LAVV, left atrioventricular valve; Pulm., pulmonary; RAVV, right atrioventricular valve; VSD, ventricular septal defect.

In addition, Table 2-1 lists some of the many other associated lesions that may be present in these complex congenital heart defects, either alone or in combination.

2.3 Historical and embryological considerations

The earliest descriptions of hearts identifiable as having a univentricular atrioventricular connection date back to the beginning of the 19th century, with an account of probable tricuspid atresia in the London Medical Review of 1812 (Anon) and Farre's description in 1814 of a heart with both atrioventricular valves draining to a single ventricular chamber. Mathey (1976) refers to an earlier description by Chemineau in 1689, although the present author was unable to substantiate this. The more famous description of an 'absent' right atrioventricular connection by Kreysig appeared in 1817 and Holmes described his eponymous heart (double inlet left ventricle with concordant ventriculo-arterial connections) in 1824. A series of observational descriptions followed during the latter part of the nineteenth century, as detailed by Rashkind (1992) and Anderson and colleagues (Anderson and Becker, 1987; Anderson et al, 1987b). The term 'double inlet' was first used by Peacock in 1855 and "atresia [of the right venous ostium]" in 1861 by Schuberg.

For most of the twentieth century there has been terminological controversy. This began with an unexplained change in emphasis from strict morphological descriptions of observed pathology, to categorising and describing hearts in terms of their *functional* status. Initially this involved the introduction of Latin terms such as 'cor triloculare biatriatum' for a (functionally) three chambered heart by Mann in 1907, despite labelling the small fourth chamber as a "(?) rudimentary right ventricle" in an illustration of the heart. Wood and Williams used the term 'cor biloculare' in 1928, and they were also the first to recognise that the mode of atrioventricular connection could be via two separate valves or a common valve. These functionally accurate Latinisms

were used into the 1950s (Anderson et al, 1987b), although in fact many of the textual descriptions included references to two ventricular chambers, one being "rudimentary" (Mann, 1907; Favorite, 1934). In 1954 Lev established the currently accepted principle of classifying cardiac chambers by their morphology, rather than by either their relative position in the cardiac mass or by the valves and vessels that entered or exited from them. This clarified the anatomic inaccuracies inherent in some earlier reports where laterality alone was used to identify a left or right ventricle (Von Rokitansky, 1875; Mann et al, 1907; Abbott, 1936).

A separate issue was the description of hearts with two ventricular chambers in which one was relatively rudimentary and the other functionally dominant. It was as early as 1939 that Taussig began the process which endeavoured to deny the rudimentary chamber ventricular status when she used the phrase, a "single ventricle with a diminutive outlet chamber" to describe a heart with double inlet left ventricle. Much confusion over nomenclature then ensued, as the terms 'single' and 'common' ventricle came into general usage. Initially, most authors used the various terms interchangeably (Abbott, 1936; Taussig, 1939; Edwards, 1960) and included hearts with all forms of the univentricular atrioventricular connection under this heading (Elliott et al, 1964). Perhaps in an attempt to clarify this, Lev and colleagues (1962) chose to differentiate between hearts with a rudimentary chamber, using the term 'single' ventricle; and those without, for which they used the term 'common' ventricle. Unfortunately, matters were clouded by the inclusion of those with a giant ventricular septal defect in this latter group; i.e., those hearts in which both left and right ventricles were identified (morphologically), but without a clearly identifiable ventricular septum.

In 1964, Van Praagh and colleagues introduced the alphanumeric scheme of classification for all 'single' or 'common' ventricle lesions, based on the above principles. Hearts with an absent atrioventricular connection however, were arbitrarily excluded. This was to become a further major source of disagreement and misunderstanding, which at times even bordered on the vitriolic (Van Praagh et al, 1982; Anderson et al, 1983; Anderson et al, 1984; Anderson and Becker, 1987). During the next 20 years, these various terms were used and further ones introduced, with no clear consensus amongst the authors as to the specific lesions covered by a particular system of classification. For instance, in contrast to most users of the alphanumeric classification, Engle (1968) included hearts with tricuspid or mitral atresia in their system. Lev and colleagues also endorsed the alphanumeric system but in 1969 they additionally promoted the term 'primitive' ventricle to cover all hearts with double inlet ventricle, in an attempt to incorporate embryological concepts, perhaps as originally implied by Campbell and co-authors in 1953. The term 'double-inlet left ventricle' itself was first coined in 1968 by de la Cruz and Miller, although primarily to describe hearts with straddling tricuspid valve chordae, such as the eponymous Lambert heart (1951).

Anderson and associates (1976) originally supported the above embryological concepts, considering hearts with double inlet ventricle to have undifferentiated primitive ventricles. They also broadened the scope of their proposals to include those hearts with an absent atrioventricular connection. As 'single ventricle' appeared to be specific to double inlet ventricle, they used the veterinary term 'univentricular' to encompass all hearts with a functional single ventricle, in fact consistent with the earlier Latinisms. It soon became apparent to these workers however, that the trabecular pattern of the

dominant ventricle was usually clearly that of a left ventricle and other previous reports had delineated a few hearts with a dominant ventricle of right ventricular morphology (Munos-Castellanos et al, 1969; Quero-Jiminez et al, 1973). The term 'primitive ventricle' was therefore dropped, in favour of the general term 'univentricular heart'. This was now redefined as "any heart in which only one chamber within the ventricular mass has an actual or potential connection with the atrial chambers" (Wilkinson et al, 1979). Unfortunately, in order to maintain the logic of 'univentricular', the denial of ventricular status to the rudimentary chamber, implicit in the widespread use of the terms 'single', 'common' or 'primitive' ventricle, was sanctified. To be given ventricular status, the chamber had to be connected to at least half of an atrioventricular junction; i.e., it had to possess an inlet component.

Further dissension and misunderstandings followed concerning what exactly constituted a ventricle when compared to an outlet chamber or pouch (Wilkinson et al, 1979; Van Praagh et al, 1979, 1982). Logic finally triumphed when Anderson and colleagues (1983) combined nineteenth century descriptive methods with morphological principles, whilst excluding embryological precepts. The words 'univentricular' and 'single' were abandoned when describing hearts with evidently two ventricular chambers, and the term 'univentricular atrioventricular connection' was introduced to accurately describe the entire group with either an absent or double inlet atrioventricular connection. It is this *connection* which is univentricular not the heart as a whole. Despite this clarification of the nomenclature and perhaps because such a heart usually does perform physiologically as a pump with only one ventricle, the earlier inaccurate terminology remains in widespread colloquial use, particularly in the

USA, although often qualified to 'single left ventricle' or 'single right ventricle' (Van Praagh, 1984).

Straddling atrioventricular valves have also been a source of disagreement over the years. Although historically such hearts have been thought to be part of the 'single ventricle' spectrum (Lambert, 1951; Taussig, 1960; de la Cruz and Miller, 1968), others have argued that they should be classified completely separately (Bharati and Lev, 1979; Van Praagh et al, 1979). This matter was resolved by simply assigning the valve to the ventricle to which it has a greater than 50% commitment (Kirklin et al, 1973), without concern over the ventricular dominance of the heart (Milo et al, 1979). Thus, if greater than 50% of both atrioventricular valves are committed to the same ventricle, then there is a double inlet atrioventricular connection to that ventricle (see Figure 2.8, page 48).

An additional important matter of terminological discord which remains unresolved refers to whether or not classic tricuspid atresia can be said to have a univentricular atrioventricular connection. Rao (1992a) has argued extensively against this concept, to the extent of dismissing it for all forms of tricuspid atresia, particularly on embryological grounds. Microscopic work by the Leiden group (Wenink and Ottenkamp, 1987) has indeed shown that a proportion of macroscopically identical tricuspid atresia specimens have a fibrous tissue strand connecting the right atrial floor to the tiny inlet component of the rudimentary right ventricle, via the central fibrous body. In some cases this point is landmarked by a macroscopic 'dimple' in the right atrial floor. This would imply the presence of biventricular concordant atrioventricular connections, as opposed to a univentricular atrioventricular connection, and

corresponds to similar findings by the same group in all the specimens that they examined with mitral atresia (Gittenberger-de Groot and Wenink, 1984). Rao (1992a) felt this to be definitive but failed to point out that a similar proportion of hearts with tricuspid atresia were found in the same study to have a fibrous connection to the dominant left ventricle, suggesting an underlying univentricular double inlet atrioventricular connection (Wenink and Ottenkamp, 1987). These Dutch authors went on to postulate that during development a sliding scale exists for the commitment of the atretic or absent tricuspid valve to either ventricle, similar to the concept for straddling valves. This concept could also be used for the mode of the atrioventricular connection itself, producing a scale from an imperforate valve, through hypoplasia with atresia, to apparent total absence of the connection (Wenink and Ottenkamp, 1987). Irrespective of these proposals, the same authors emphasised that in a practical clinical setting, there remains an absent atrioventricular connection and that this term should be preferred, as only microscopic examination can distinguish the various forms involved. This latter view was in fact supported by Gessner (1992) in the same book as Rao's chapter (1992a), when emphasising the embryological implications and hypotheses surrounding these issues. It should be noted that these macroscopic difficulties are compounded by a later finding in a multicentre study that only a minority of such hearts with tricuspid atresia (33 out of 97) had a right atrial dimple (Thoele et al, 1991).

In 1991 Anderson summarised these arguments to facilitate a practical and pragmatic way forward by distinguishing the approaches of the clinician, morphologist and embryologist. The term tricuspid atresia should be used, but with the implicit understanding that the two words represent a broad spectrum of possible anomalies which need to be detailed before embarking on treatment of the individual patient.

Similarly, alphanumeric classifications (Van Praagh et al, 1964; Rao, 1992c), which have continued to expand to impractical multiple levels of hierarchy to incorporate rare but important varieties, should be abrogated in favour of the above descriptive morphological approach, as detailed in Section 2.2 above (page 41).

2.4 Isomerism of the atrial appendages and visceral heterotaxy

More recently a new debate has emerged with particular relevance to patients with double inlet ventricle: the clinical and morphological recognition of the subtypes of visceral heterotaxy with respect to right and left atrial isomerism. One quarter of the current series of patients with double inlet ventricle had these associated malformations of situs (see page 81). Again there is a division in the views between the Boston group (Van Praagh and Van Praagh, 1990) and the "European School" (Anderson, 1995, 1996). The dispute revolves around the criteria used to distinguish between a morphologically right and morphologically left atrium and whether right and left isomerism of the atrial appendages exists as part of the heterotaxy syndromes.

The Boston group believe that atrial situs can only be either solitus (i.e., the usual atrial arrangement) or its mirror-image. In other words, there must always be a morphologically right and morphologically left atrium present, never two right atriums or two left atriums in the same heart. They argue that embryologically the heart does not acquire right and left organisation until relatively late in development. In contrast, both groups agree that the lungs and bronchi do exhibit isomerism in the heterotaxy syndromes. The Boston group base their criteria of diagnoses on firstly, the venoatrial

connections including the coronary sinus drainage and then secondly, on the size and shape of the atrial appendages (Van Praagh and Van Praagh, 1990). Thus, the right atrium is considered the atrium which receives all of the systemic veins, as well as having a normal coronary sinus and some, all or none of the pulmonary veins. The left atrium is either characterised by finding half or all of the pulmonary veins connecting to it and none of the systemic veins (except in the setting of a left superior caval vein and a co-existent unroofed coronary sinus); or it is designated as the left atrium given the positive identification of a right atrium. Where these criteria are not present, the atrium with the larger sized and more anteriorly positioned appendage is "likely" to be the right atrium. Even using these multiple criteria however, it was not possible for these workers to identify the atrial situs in 19% of "asplenia syndrome" specimens in a series of 109 post-mortem cases of visceral heterotaxy (Van Praagh et al, 1990). Furthermore, the use of these criteria with various exclusions and possibilities, is inconsistent with the Boston group's own "morphological method" (Lev, 1954; Van Praagh et al, 1964). This states that structures should be identified according to the component part that is most consistently present. This would exclude the venoatrial connections and features of the atrial septum in these complex patients, as they are very often abnormal or completely absent. The features that are most universally present are the atrial appendages with their distinct internal anatomy (see below) and it is not clear as to why these are only used as secondary arbiters by these workers.

In contrast, the European school believe in the concept of atrial appendage isomerism, whilst agreeing that the atriums as a whole are not truly isomeric (Anderson, 1995). The atrial appendage shape and the distribution of the pectinate muscles are used to distinguish the right and left atriums (Sharma et al, 1988), as detailed in Section 2.1

(page 33) and Table 2-1. Each atrium is identified by observing definite anatomic features, and not by indirect inference. These criteria were successfully used in a recent series of 183 post-mortem cases with visceral heterotaxy, to clearly demonstrate isomerism of the right and left atrial appendages (Uemura et al, 1995b). The same series also confirmed the inconsistency of the splenic status and venoatrial connections in these patients, when correlated with the isomeric status of the atrial appendages, bronchi and lungs (Uemura et al, 1995a).

It seems likely that this debate will continue, but at present the European method appears to be of more practical use, particularly as advances in echocardiography are now enabling atrial appendage morphology to be imaged ever more clearly. Although the term isomerism is perhaps not totally accurate, in that the size and position of the appendages with respect to each other are not identical, due at least in part to foetal haemodynamic flow influences (Van Praagh et al, 1990), this appears to be a minor inconsistency when compared to the other factors discussed above. Even where the appendage morphology is clear, the inconsistencies of the accompanying morphological abnormalities dictate that it remains crucial to identify and describe all elements of the malformed heart and visceral organs, including the venoatrial connections and splenic status, so that a comprehensive plan of management for the individual patient can be formulated.

Chapter 3

Materials and methods

3.1 Patient populations

This study examines retrospectively the fate of 428 consecutive patients with double inlet ventricle and tricuspid atresia who presented in the first year of life to two tertiary paediatric cardiac centres in London: the Great Ormond Street Hospital for Children (264 patients) and the Royal Brompton Hospital (164 patients). The clinical progress, operative details and outcome of the patients were determined from their medical records and by contacting the family or family physician. Operative mortality was defined as death during the whole post-operative, in hospital period.

The patients were divided into three groups for detailed analysis:

I. Patients with double inlet ventricle: 191 consecutive infants (107 male and 84 female) who presented within the first year of life between January 1973 and May 1985. They represented approximately 70% of patients of all ages who presented with double inlet ventricle to the two institutions. The age of initial presentation to the tertiary centre was from one to 270 days (median three days) and the duration of follow-up was from 0.4 to 16.2 years (median 8.5 years). Only five patients were lost to follow-up (2.5%).

II. Patients with tricuspid atresia: 237 consecutive infants (124 male and 117 female) who presented within the first year of life between January 1972 and December 1987. They represented approximately 95% of patients of all ages who presented with tricuspid atresia to the two institutions. The age of initial presentation to the tertiary centre was from one to 362 days (median 24 days) and the duration of follow-up was from 0.4 to 17.3 years (median 8.0 years). Only seven patients were lost to follow-up (3%).

III. Patients at risk of having or developing subaortic stenosis: a combined sub-group of 102 consecutive infants from those in the above two cohorts: 56 with double inlet ventricle and 46 with tricuspid atresia. This group consisted of all those with the morphological substrate particularly prone to having or developing subaortic stenosis: a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow. Patients with aortic valve stenosis or atresia were excluded. The mean duration of follow-up was 8.5 years.

3.2 Morphological criteria and definitions

The morphological characteristics of the patients were described by means of the sequential segmental approach, using the terminology of Anderson and colleagues (1984, 1987c). The definitions used with respect to the presence of a univentricular atrioventricular connection are detailed in Chapter 2 (pages 41-57). Patients with an absent left atrioventricular connection ('mitral atresia') and those with a huge ventricular septal defect were excluded from the study. The four patients with a double

inlet atrioventricular connection and an imperforate right atrioventricular valve were included exclusively in the double inlet group to avoid duplication.

The morphological diagnosis was confirmed or established by examining cineangiograms, intra-operative reports and autopsy specimens. Cross sectional echocardiograms were reviewed in patients who presented after 1980 using the guidelines of Rigby and colleagues (1981). Atrial situs was occasionally determined by using penetrated chest x-rays to determine the bronchial situs, as this almost invariably corresponds to the arrangement of the respective atriums (Deanfield et al, 1980).

Subaortic obstruction was considered present when there was either a resting gradient of greater than 10 mmHg across the systemic outflow tract from the left ventricle to the aortic valve at catheterisation or by Doppler interrogation; or when the size of the ventricular septal defect was less than half of the diameter of the aortic valve, at end-systole; or both. No attempt was made to induce a gradient using inotropic infusions. Ratios of the ascending aorta size to that of the pulmonary trunk and the ventricular septal defect were determined by measuring arterial diameters at the level of the basal attachment of the leaflets of the semilunar valve and the end-systolic diameter of the ventricular septal defect. These measurements were made using the angiographic projection or cross sectional echocardiographic plane that best profiled the ventricular septal defect or great artery, at end-systole.

Pulmonary arteries with a diameter of three millimetres or less at initial investigation or surgery were considered hypoplastic.

In patients with tricuspid atresia, 'effective' pulmonary atresia was defined by either the presence of pulmonary valvar or infundibular atresia or when the ventricular septum was intact in the presence of concordant ventriculo-arterial connections. Throughout the tricuspid atresia analyses, these patients were grouped together with those whose ventriculo-arterial connection was a single outlet with pulmonary atresia.

3.3 Haemodynamic definitions

Pulmonary blood flow at initial presentation to the tertiary centres was determined by cardiac catheterisation. A calculated pulmonary to systemic flow ratio (Q_p:Q_s) of over 1.5:1 was considered high flow; less than 1:1, low flow; and between 1:1 and 1.5:1, balanced flow. When no invasive investigation was undertaken, clinical evaluation in combination with chest radiography was used for this purpose. A restrictive atrial communication was diagnosed when an 'a' wave gradient of over 5 mmHg or a 'mean' gradient of over 3 mmHg was present between the atriums.

3.4 Suitability for definitive surgery

The morphological and physiological data from all the patients were examined retrospectively with a view to suitability for definitive surgery by a Fontan-type operation. In addition, data from those patients with double inlet ventricle were studied with respect to suitability for definitive surgery by a ventricular septation procedure.

3.4.1 Fontan-type procedure

The criteria used for considering a patient to be suitable for a Fontan-type procedure were based on those of Choussat and colleagues (1977) with modifications as suggested by Mayer and associates (1986) and Danielson (1987). Thus, the presence of any of the following features at the time of first being assessed at the tertiary centre excluded the patient from future consideration for a Fontan-type procedure: a pulmonary arteriolar resistance of greater than 2 units.m^2, systemic outflow obstruction at valvar or subvalvar level, moderate to severe regurgitation of the future systemic atrioventricular valve or marked dysfunction of the dominant ventricle (as judged by echocardiographic and/or angiographic review).

Anomalous systemic and pulmonary venous connections were not considered contra-indications to repair, unless the surgeon at the time felt that they precluded adequate separation of the venous returns. This may not have been established until eventual atriotomy. Similarly, only patients with a degree of pulmonary arterial distortion that the surgeon at the time felt unable to reconstruct, were considered not to be candidates for future definitive repair.

In addition, patients who presented with complex cardiovascular anomalies that would have required multiple high risk palliative procedures to reach a stage when a Fontan-type procedure could be considered, were also deemed to be unsuitable candidates. This was despite meeting theoretical anatomical and haemodynamic criteria.

3.4.2 Ventricular septation operation

This procedure can only be performed for double inlet ventricle patients. The guidelines of Bargeron (1987) and Pacifico (1986) were used to establish suitability for a 'low risk' ventricular septation procedure. Thus, a patient was considered suitable only if the following anatomical features were found when first assessed at the tertiary centre: a dominant ventricle of left or indeterminate morphology; two normal atrioventricular valves; ventriculo-arterial connections which were either discordant or double outlet from the dominant ventricle, with the aorta anterior and to the left of the pulmonary root; and only mild or absent pulmonary outflow obstruction. Patients with a common atrioventricular valve, double inlet right ventricle or systemic outflow obstruction at valvar or subvalvar level, were not considered to be candidates for such surgery. In addition patients who would require either atrioventricular valve replacement, the construction of a 'right' ventricle to pulmonary arterial conduit, an atrial rearrangement procedure (due to the aorta being anterior and rightward of the pulmonary trunk), or a combination of any of these features; were all considered unsuitable for a ventricular septation procedure due to the high operative risk of 36% to 47% (Feldt et al, 1981; Stefanelli et al, 1984; Pacifico, 1986; Bargeron, 1987). The atrioventricular valvar anomalies which were considered to be sufficiently severe to mandate valve replacement were stenosis or marked regurgitation of either valve and the presence of straddling of the tension apparatus where it crossed the dominant left ventricle; for example, straddling of the right sided atrioventricular valve to a left sided rudimentary right ventricle.

3.5 Statistical methods of analysis

A multistage statistical analysis was performed separately for the two morphologically distinct populations: those with double inlet ventricle and those with tricuspid atresia. A further analysis focused on the problem of subaortic stenosis (see section 3.5.5 below).

The primary interests of the study were twofold. Firstly, to try and assess the natural history of the lesions, whilst acknowledging that during the period of study surgical interventions would have been used whenever considered necessary. Secondly, to establish the influence of the underlying morphology and haemodynamics on survival and subsequent suitability for definitive surgery, whilst taking into account the various management strategies used for different patient sub-groups. Survival, hazard and risk factor analyses were therefore largely restricted to the time period before definitive surgery, so as to achieve some understanding of survival without the added influence of the changing techniques of definitive surgery during the study period. Quoted 'relative risks' were obtained by treating 'definitive surgery' as an event leading to withdrawal of the patient from further follow-up, such that the patient was 'censored' as alive at this point in time. Hence, the outcome period was until the time the patient was last traced or seen, or until the date of a definitive operation. Definitive surgery was effectively treated as an event with unknown consequence.

There were four stages to these analyses:

1. A description of the overall survival of the patients.

2. A three stage mortality risk factor analysis using the various morphological and haemodynamic factors found at the time of first being assessed by the tertiary centre. Palliative surgical events were ignored in this analysis, whilst the era and age of initial presentation were included.

3. A description of survival following palliative surgery. This was followed by an attempt, for double inlet ventricle patients only, to analyse the effects of palliative operations on the underlying natural history. This was achieved by comparing the outcomes of those who underwent such surgery with those who did not, whilst incorporating the effects of the above risk factors.

4. An examination in three stages of the patients' suitability for definitive surgery: at initial presentation, during subsequent follow-up and during follow-up whilst incorporating the above risk factors (for tricuspid atresia patients only). The effects of medical and palliative surgical management strategies on suitability were ascertained and then used to infer an optimal age range between which definitive surgery might be undertaken.

3.5.1 Survival analyses

In all analyses, time zero was the time of birth. Overall time-related survival (freedom from death) was determined by the Kaplan-Meier method (1958). Interest was focused on a second analysis of survival, in which patients were 'censored as alive' and withdrawn from further follow-up at the time of a definitive operation (see above). This censored analysis *did not exclude* patients at the time of a palliative procedure.

Time related hazard rates (i.e., the instantaneous monthly risks of death) were also estimated prior to definitive surgery, at increasing ages.

3.5.2 Risk factor analyses

A list of potential morphological and physiological risk variables (or 'factors') for death in this censored analysis was compiled separately for patients with double inlet ventricle and tricuspid atresia (Tables 4-3 and 5-3, pages 89 and 133). Each variable consisted of a list of possible categories and a particular category was then selected to act as a *baseline category* for later analysis. This usually was the most common category numerically and thus corresponded to the most 'normal' category with respect to the 'average' patient with either double inlet ventricle or tricuspid atresia. The main exception to this was that the category 'after 1979' was arbitrarily chosen as the baseline category for the 'era of presentation' variable, so as to be closest to the current era. The relation of these variables to survival was explored using the Cox proportional hazards (semi-parametric) method (Cox and Oakes, 1985). This calculation provided a Cox-coefficient for each non-baseline category, which when exponentiated ($e^{coefficient}$), gave the relative risk (proportional increase in monthly risk of dying) associated with that category relative to its baseline category. These were estimated with 95% confidence intervals. There were three stages to this analysis:

i) A univariate analysis was performed to assess the relative effects on survival of each category within each variable, in isolation from the other variables. The most common category was usually used as the baseline category against which the other categories

were compared (see above). Thus, the resulting relative risks expressed the proportional increase in 'hazard' (monthly risk of dying) associated with a particular category versus the baseline category, and were estimated with 95% confidence intervals.

ii) A multivariate analysis simultaneously estimated the relative risks for all the concomitant variables, to yield a new relative risk for each category. The results for the categories within individual variables could not (by definition) be interpreted in isolation, but by multiplying together the individual relative risks of appropriate combinations of categories from all of the variables, an overall assessment of risk for the different variants of double inlet ventricle or tricuspid atresia was generated. Estimated survival curves for these variants, from birth through to definitive surgery were then created, using the method described in Appendix A (page 224). As stated, these estimates of rates of survival referred to a hypothetical cohort in which definitive surgery was deemed to be an event with unknown consequence.

iii) To aid clinical use, a simpler additive index was subsequently derived from these results by rounding the natural logarithm of the estimated multivariate relative risks (i.e., the Cox coefficient) to the nearest integer. As for the multiple risk factor analysis, each score could not be used in isolation, but their sum for an individual patient produced an 'additive index score' for that patient. This total score could be exponentiated to give the approximate overall relative risk for that patient, relative to an individual with all the baseline categories, as derived from the above multivariate analysis. The higher the additive score, the greater the risk of death. The 191 double inlet ventricle patients and 237 tricuspid atresia patients were then stratified retrospectively into groups, based on their total additive scores. A cross tabulation was

then generated of these scores against the respective actual patient outcomes. The predictive ability of each additive index was validated by comparing these results with the multiplicative multivariate analysis.

3.5.3 Effects of palliative surgery

Actuarial survival and hazard rates were determined, in order to compare outcomes for patients undergoing the three main palliative surgical procedures: construction of a systemic-to-pulmonary arterial shunt, isolated banding of the pulmonary trunk and repair of the aortic arch together with banding of the pulmonary trunk. This was undertaken separately for the patients with double inlet ventricle and those with tricuspid atresia. As before, the patients were censored as being alive at the time of definitive surgery.

For patients with double inlet ventricle only, the multivariate analysis previously undertaken to establish the risk factors for death was repeated. The same variables were used, but in addition the relative risks of palliative surgery overall, and the three main palliative procedures described above, were incorporated into the computations. This led to the risks associated with palliative surgery being adjusted by the previously analysed factors found at initial assessment. Then, three time-varying covariates were introduced into the analysis, such that they were 'turned on' and 'turned off' again within particular time periods (Cox and Oakes, 1985; Appendix B, page 230). For instance, the immediate post-operative risk was assessed by introducing a variable that turned on at the time of the palliative operation and turned off again one month later. This technique allowed patients of a similar age and with a similar underlying total

relative risk, but who had not yet received surgical palliation, to act as simultaneous 'controls'. The same analysis was then repeated for two further time periods to assess post-operative outcome in both the short term (one to six months) and medium term (greater than six months). Finally, in order to investigate the robustness of the above additive index, the index was recalculated to include the palliative surgical risk factors described above and the two tables were compared.

3.5.4 Suitability for definitive surgery

This was examined by retrospective analysis in two stages: at the time of initial assessment at the tertiary centre and during subsequent follow-up.

i) The initial morphological and physiological data for each patient were reviewed to determine the potential suitability for eventual definitive repair at the time of initial presentation to the tertiary centre. Information obtained later in life that was present but undiagnosed when first seen, was also used to decide suitability (for example, complex anomalies of systemic and pulmonary venous return). The patients consequently fell into two mutually exclusive groups: those considered to be potentially suitable for a future Fontan-type procedure and those considered to be already unsuitable for the operation. A third group of double inlet ventricle patients, not mutually exclusive to those suitable for Fontan-type surgery, was delineated as those considered to be potentially suitable for a future 'low risk' ventricular septation operation. All patients considered to be suitable for surgery by a ventricular septation procedure were also candidates for a Fontan-type operation. Actuarial survival curves for each of the

groups were then determined and compared, again censoring the patients as alive at the time of definitive surgery.

ii) Within this framework, the outcomes of the potentially suitable patients were examined with respect to death and the development of new adverse features that would preclude definitive surgery, taking into account the various surgical and medical management strategies undertaken in infancy. An arbitrary cut off point of 1.5 years for the patients with tricuspid atresia and two years for the patients with double inlet ventricle, was taken as the youngest age at which elective definitive repair would be considered *during the period under study.* The potential for definitive surgery in survivors beyond this age and prior to definitive surgery was established by cardiac catheterisation and angiography. Those who had not yet been recatheterised by the end of the study period and those who had not reached this age when last seen were considered potential candidates for repair, unless they had already been shown to be unsuitable by earlier investigation(s). Actuarial curves prior to definitive surgery for survival free of new adverse features, which would preclude a Fontan-type procedure or a ventricular septation operation (for patients with double inlet ventricle), were created. Outcomes after the different management strategies undertaken in infancy were then compared using the non-parametric chi-squared test.

In addition, for patients with tricuspid atresia, the multivariate risk factor analysis was repeated, but using the additional end-point of suitability for a Fontan-type procedure. This also produced a new additive index and cross tabulation of scores against actual patient outcome.

3.5.5 Analyses for patients at risk of having or developing subaortic stenosis

These 102 patients fell into three groups, as determined by the anatomy found when first assessed at the tertiary centres: those with subaortic stenosis with or without aortic arch obstruction, those without subaortic stenosis but with aortic arch obstruction and those without either subaortic stenosis or aortic arch obstruction. Actuarial survival curves were created and compared for the latter two groups, using freedom from subaortic stenosis and death as adverse outcome measures. As before, the patients were additionally censored as being alive at the time of definitive surgery in order to examine the effects of palliative surgery on survival. The ratios at initial investigation at the tertiary centres, of the ascending aorta diameter to the diameter of the ventricular septal defect and separately, the ascending aorta diameter to the diameter of the pulmonary trunk, were ascertained retrospectively for each of the three groups. These ratios were evaluated with reference to the presence or development of subaortic stenosis during the follow-up period. The differences between the means of these samples were then compared using the parametric student's *t*-test.

Chapter 4

Results of the 191 patients with double inlet ventricle

4.1 Morphology

Patients with double inlet ventricle were found to have a high frequency of abnormal atrial arrangement (Table 4-1, Figure 4.1), particularly when compared to those with tricuspid atresia, nearly all of whom had the usual atrial arrangement (Chapter 5, page 124). A common atrioventricular orifice was particularly associated with an abnormal atrial arrangements, such that all but one patient (97%) with right isomerism of the atrial appendages, 11 patients (79%) with left isomerism of the atrial appendages and all of those with mirror-image arrangement, had a common atrioventricular valve (Figure 4.1). The majority of patients (136 patients, 71%) had double inlet to a dominant left ventricle, but 34 patients (18%) had double inlet to a morphological right ventricle and 21 patients (11%) had double inlet to a ventricle of indeterminate morphology. Most patients with double inlet right ventricle or double inlet to a ventricle of indeterminate morphology had a common atrioventricular valve (Table 4-1, Figure 4.1). In double inlet left ventricle, discordant ventriculo-arterial connections were most common (82 patients, 60%; Table 4-1), whilst in those with a dominant ventricle of right or indeterminate morphology, double outlet from the dominant or solitary ventricle predominated: 19 out of 31 patients (56%) and 14 out of 21 patients (67%), respectively. A single outlet from the heart was present in 42 patients (22%; Table 4-1).

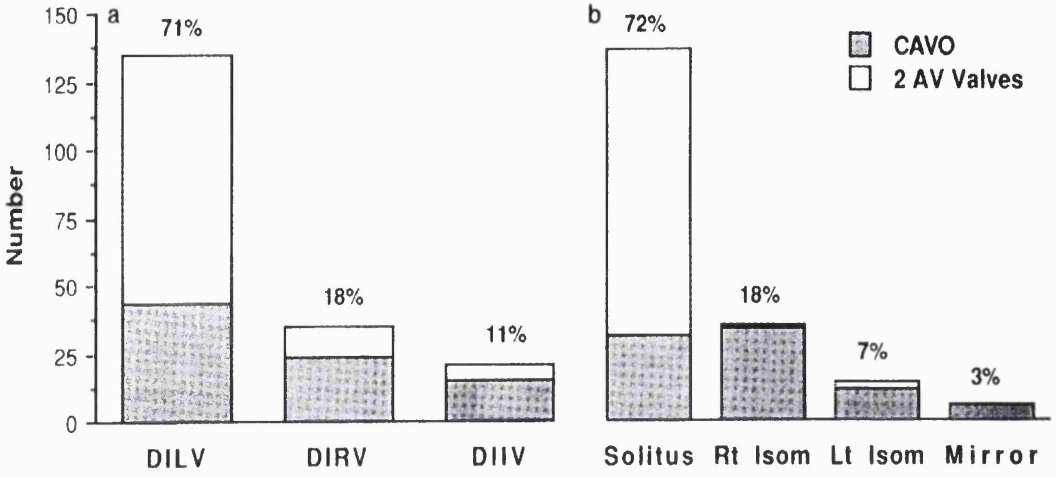

Figure 4.1. Histograms showing the mode of atrioventricular connection for the 191 patients with double inlet ventricle with respect to **a)** the morphology of the dominant ventricle and **b)** the atrial arrangement. A common atrioventricular orifice was present in 42% of the 191 patients.

AV, atrioventricular; CAVO, common atrioventricular orifice; DIIV, double inlet indeterminate ventricle; DILV, double inlet left ventricle; DIRV, double inlet right ventricle; Lt Isom, left atrial isomerism; Mirror, mirror image atrial arrangement; Rt Isom, right atrial isomerism; Solitus, situs solitus (i.e., the usual atrial arrangement).

A variety of associated lesions were also found at initial presentation, as detailed in Table 4-2. Of note was that 34 out of the 191 patients (18%) had systemic arterial obstruction at subvalvar, valvar or great arterial level. Extracardiac anomalous pulmonary venous connections were present in 28 infants (15%), all but three of whom had right atrial isomerism (two patients had left atrial isomerism and one had the usual atrial arrangement).

Table 4-1. Morphology and haemodynamics found in the 191 patients with double inlet ventricle at initial presentation

	Ventricular morphology			
	DILV N = 136	DIRV N = 34	DIIV N = 21	Total (%)
Atrial arrangement				
Usual (situs solitus)	113	17	7	137 (72)
Right atrial isomerism	15	11	8	34 (18)
Left atrial isomerism	4	5	5	14 (7)
Mirror-image (situs inversus)	4	1	1	6 (3)
Mode of atrioventricular connection				
Two atrioventricular valves	94	11	5	110 (58)
Common atrioventricular valve	42	23	16	81 (42)
Ventriculo-arterial connections				
Concordant	16	1	0	17 (9)
Discordant	82	3	0	85 (44)
Single outlet:				
Pulmonary atresia: aorta from the dominant ventricle	18	10	5	33 (17)
Pulmonary atresia: aorta from the rudimentary ventricle	5	0	0	5 (3)
Aortic atresia: pulmonary trunk from the dominant ventricle	0	1	2	3 (1)
Common arterial trunk	1	0	0	1 (1)
Double outlet:				
from the dominant ventricle	11	19	14	44 (23)
from the rudimentary ventricle	3	0	0	3 (2)
Pulmonary blood flow				
Low flow	52	22	13	87 (46)
High flow	73	9	4	86 (45)
Balanced flow	11	3	4	18 (9)

DIIV, double inlet indeterminate ventricle; DILV, double inlet left ventricle; DIRV, double inlet right ventricle.

Table 4-2. Associated lesions found in the 191 patients with double inlet ventricle at initial presentation

	Ventricular morphology		
	DILV	**DIRV**	**DIIV**
Atrioventricular valvar anomalies			
Straddling right AV valve	11	0	0
Straddling left AV valve	5	1	0
Stenosed right AV valve	3	0	0
Stenosed left AV valve	4	2	0
Imperforate right AV valve	3	0	1
Imperforate left AV valve	1	0	1
Supravalvar left AV valve membrane	1	0	0
	33 patients (17%)		
Systemic arterial obstruction			
Isolated coarctation of aorta	17	0	1
Isolated interrupted aortic arch	4	0	0
Arch obstruction & subaortic stenosis	8	0	0
Isolated subaortic stenosis	2	0	0
Aortic valvar & subvalvar stenosis	2	0	0
	34 Patients (18%)		
Pulmonary stenosis			
Isolated pulmonary valvar stenosis	22	8	7
Isolated pulmonary subvalvar stenosis	11	1	2
Pulmonary valvar & subvalvar stenosis	19	6	0
	76 Patients (40%)		
Pulmonary arterial distortion or hypoplasia			
Pulmonary arterial stenosis(es)	5	1	0
Interruption of right pulmonary artery	1	0	1
Severely hypoplastic pulmonary arteries	5	3	2
	18 Patients (9%)		
Extracardiac anomalous pulmonary venous connections			
Totally APVC: not obstructed	5	4	3
Totally APVC: obstructed	4	0	4
Partially APVC	3	2	2
Pulmonary venous atresia	0	0	1
	28 Patients (15%)		

AV, atrioventricular; APVC, anomalous pulmonary venous connections; DIIV, double inlet indeterminate ventricle; DILV, double inlet left ventricle; DIRV, double inlet right ventricle.

A combination of these associated lesions (defined as the presence of more than one associated lesion or one associated lesion combined with a single outlet from the heart, excluding pulmonary valvar or subvalvar stenosis), was found in 47 patients (25%), as discussed below (Section 4.6, page 105). The classical morphological pattern of the usual atrial arrangement, double inlet left ventricle, two atrioventricular valves and discordant ventriculo-arterial connections, with no other associated anomalies other than valvar or subvalvar pulmonary stenosis (15 patients), was found in 37 children (19%) overall.

4.2 Clinical presentation

The mode of initial presentation to the tertiary centres was related to the amount of pulmonary blood flow and to the presence of significant associated lesions. The 87 patients (46%) with marked cyanosis and reduced pulmonary blood flow presented at a median age of one day (range 1-270 days), with 66 of these infants (78%) presenting at less than one week of age. This was significantly earlier than those with high or balanced pulmonary flow ($p < 0.0001$: Wilcoxon signed-ranks test). The median age of initial presentation of the 86 patients (45%) with high pulmonary flow, cardiac failure and mild cyanosis was similar to the 18 asymptomatic patients (9%) with balanced pulmonary blood flow: median ages ten and seven days (ranges 1-240 and 1-180 days) respectively. Twenty three of the 191 infants (12%) presented with additional low output cardiac failure and acidosis in the first week of life (pH of less than 7.20 for over six hours). This was due in most cases to the presence of severe associated lesions: 11 patients had systemic arterial obstruction, four had extracardiac totally anomalous

pulmonary venous connections and nine infants had a combination of such lesions (see Section 4.6, page 105).

Electrocardiographic findings were unhelpful in diagnostic terms, but two patients were found to have complete heart block and two had Wolff-Parkinson-White syndrome at initial assessment.

4.3 Overall survival

Overall survival, including all operated patients, was 57% at age one year, 40% at age five years and 35% at age ten years (Figure 4.2).

When the patients were withdrawn (censored) as alive at the time of their definitive operation, the survival rate was 43% at age five years and 42% at age ten years (Figure 4.2, upper curve). The hazard rate (monthly risk of death) prior to definitive surgery decreased dramatically over the first year of life (Figure 4.3), and then persisted at a lower rate throughout follow-up.

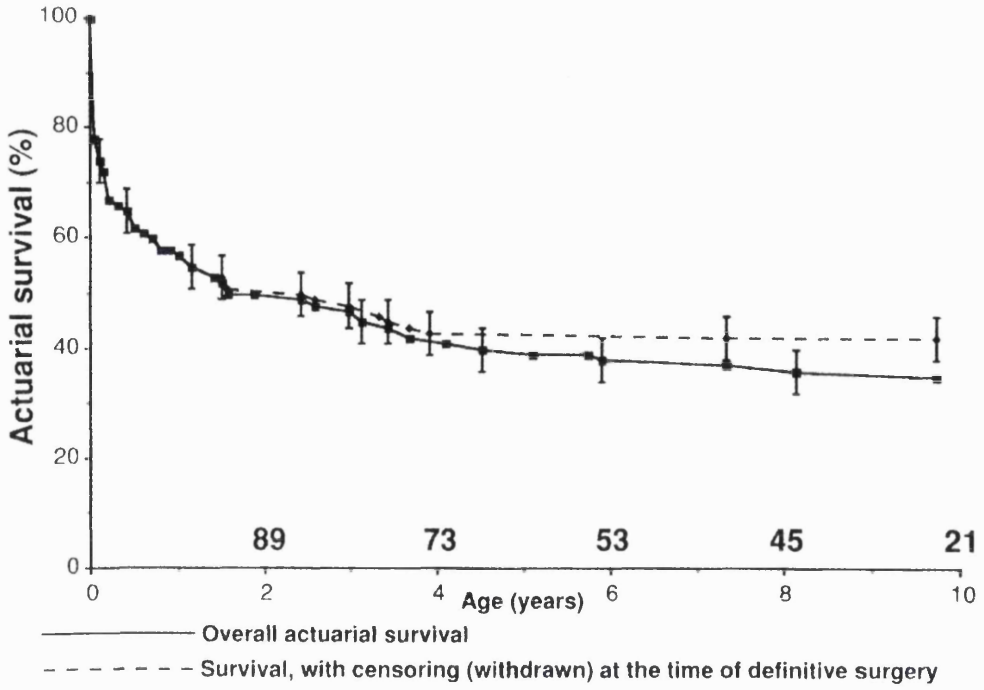

Figure 4.2. Kaplan-Meier actuarial survival curves for the 191 patients with double inlet ventricle. The upper dashed curve refers to the survival of the patients before definitive surgery (i.e., the patients were 'censored' as alive at the time of definitive surgery; see Chapter 3, page 73). The vertical bars are the actuarial 70% confidence limits, and the numbers are the remaining patients still being followed at that time, with reference to the time scale of the x-axis.

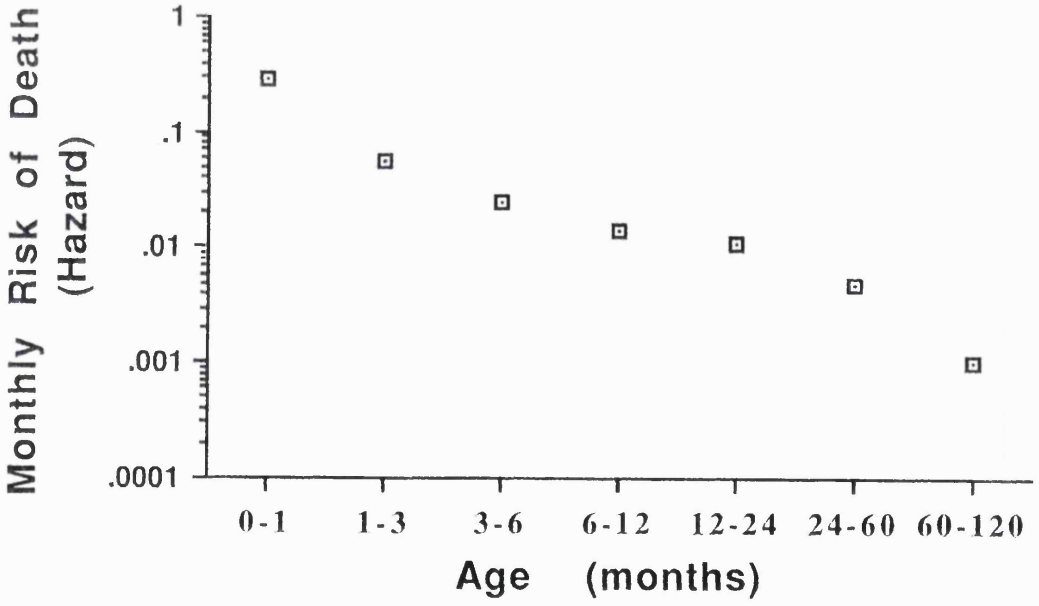

Figure 4.3. Hazard function for death (instantaneous monthly risk of death), using a logarithmic scale, during different age brackets for the 191 patients with double inlet ventricle. There was virtually an exponential decline in the monthly risk over time.

4.4 Risk factor analyses

Univariate analysis established that each of the following six categories had a relative risk of mortality of greater than two: right atrial isomerism, a common atrioventricular valve, a single outlet ventriculo-arterial connection (pulmonary atresia, aortic atresia or common arterial trunk), obstruction of the systemic outflow at any level, extracardiac anomalous pulmonary venous connections and severe acidosis at initial presentation. In other words, each of these categories had a monthly risk of mortality at least twice that of its respective baseline category within each variable (Table 4-3). In contrast, the presence of any of the three categories pulmonary valvar or subvalvar stenosis, balanced pulmonary blood flow when first seen and an initial presentation at greater than two weeks of age; each reduced the relative risk of death by at least half when compared to its respective baseline category within each variable (Table 4-3). These results are exemplified by the unadjusted percentage survival figures for the patients who had a particular risk factor category within each variable, up until the time of definitive surgery (Table 4-3, column 2).

The results of the multivariate analysis gave a more accurate picture of the individual patient who evidently had a 'combination of variables'. To explore the effects and relative strengths of the risk factors further, the total relative risks of seven hypothetical patients with particular common variants of double inlet ventricle were related to a 'baseline' patient who was defined as having all of the baseline categories.

Table 4-3. Risk factor analysis for the 191 patients with double inlet ventricle, using factors as found at initial presentation - I

Variable and categories	N	%	Percentage Survival (mean ± SEM) at 2 years	at 5 years	Univariate relative risk (95% CL)	Multivariate relative risk (95% CL)
Atrial arrangement (situs)						
Usual (solitus) †	137	72	56 ± 4	49 ± 4	**p < 0.0001**	**p = 0.02**
Mirror-image (inversus)	6	3	66 ± 19	33 ± 19	1.15 (0.42, 3.15)	0.47 (0.14, 1.60)
Right isomerism	34	18	17 ± 6	14 ± 6	2.94 (1.90, 4.54)	1.45 (0.71, 2.95)
Left isomerism	14	7	65 ± 13	57 ± 13	0.72 (0.31, 1.65)	0.38 (0.14, 1.01)
Dominant ventricular morphology						
Left †	136	71	53 ± 4	47 ± 4	**p = 0.10**	**p = 0.13**
Right	34	18	25 ± 10	25 ± 10	1.82 (1.04, 3.18)	0.54 (0.29, 0.99)
Indeterminate	21	11	52 ± 9	39 ± 9	1.19 (0.73, 1.94)	0.81 (0.38, 1.71)
Mode of atrioventricular connection						
Two atrioventricular valves †	110	58	61 ± 5	53 ± 5	**p = 0.002**	**p = 0.30**
Common atrioventricular valve	81	42	36 ± 5	30 ± 5	2.03 (1.39, 2.98)	1.35 (0.77, 2.37)
Ventriculo-arterial connections						
Discordant †	85	44	65 ± 5	58 ± 6	**p < 0.001**	**p = 0.01**
Concordant	17	9	54 ± 11	42 ± 12	1.52 (0.77, 2.99)	1.85 (0.89, 3.87)
Pulmonary atresia ‡	38	20	23 ± 7	18 ± 6	3.39 (2.08, 5.53)	1.93 (0.57, 6.51)
Aortic atresia / truncus	4	2	0	0	20.80 (6.77,63.95)	4.73 (1.16,19.28)
Double outlet ‡	47	25	49 ± 8	42 ± 8	1.62 (0.97, 2.70)	3.40 (1.64, 7.06)
Pulmonary valvar and/or subvalvar obstruction						
Absent †	115	60	36 ± 4	29 ± 4	**p < 0.0001**	**p = 0.03**
Present	76	40	71 ± 5	63 ± 6	0.35 (0.22, 0.54)	0.35 (0.13, 0.92)
Systemic outflow obstruction						
Absent †	157	82	56 ± 4	49 ± 4	**p < 0.0001**	**p = 0.01**
Present	34	18	22 ± 7	15 ± 6	2.45 (1.58, 3.80)	2.33 (1.25, 4.32)

Table 4-3. Risk factor analysis for the 191 patients with double inlet ventricle, using factors as found at initial presentation - II

Variable and categories	N	%	Percentage Survival (mean ± SEM) at 2 years	at 5 years	Univariate relative risk (95% CL)	Multivariate relative risk (95% CL)
Anomalous pulmonary venous connections						
Absent (normal) †	163	85	56 ± 4	49 ± 4	**p < 0.0001**	**p < 0.0001**
Present	28	15	14 ± 7	10 ± 6	3.12 (1.98, 4.92)	4.83 (2.41, 9.72)
Pulmonary blood flow at presentation						
High †	86	45	51 ± 5	43 ± 6	**p = 0.04**	**p = 0.23**
Low	87	46	44 ± 5	37 ± 5	1.20 (0.81, 1.77)	1.28 (0.46, 3.56)
Balanced	18	9	71 ± 11	71 ± 11	0.40 (0.16, 1.00)	0.51 (0.15, 1.65)
Severe acidosis at presentation						
No acidosis †	168	88	57 ± 4	49 ± 4	**p < 0.0001**	**p < 0.0001**
Acidosis present	23	12	0	0	25.60 (12.90,50.86)	16.56 (7.36,37.32)
Age at initial presentation						
Less than two weeks of age †	129	67	40 ± 4	29 ± 4	**p < 0.0001**	**p < 0.003**
Two weeks to two months of age	36	19	62 ± 8	49 ± 7	0.42 (0.24, 0.75)	0.54 (0.29, 1.00)
After two months of age	26	14	85 ± 7	69 ± 7	0.18 (0.07, 0.44)	0.23 (0.09, 0.60)
Era of initial presentation						
After 1979 †	77	40	58 ± 6	46 ± 6	**p = 0.12**	**p = 0.001**
Prior to 1980	114	60	45 ± 5	41 ± 6	1.37 (0.92, 2.03)	2.16 (1.36, 3.42)

† Baseline category

‡ Both ventriculo-arterial outlets, or the sole great artery, may arise from either the dominant or rudimentary ventricle.

CL, confidence limits; SEM, standard error of the mean; Truncus, common arterial trunk.

To calculate the total relative risk of a patient with a particular variant of double inlet ventricle at initial presentation, all of the relative risks for that patient are multiplied together. See page 91 for an example.

An estimated survival curve can then be produced using the methodology detailed in Appendix A (page 224).

To calculate the total relative risk of a patient with a particular variant of double inlet ventricle at initial presentation, all of the relative risks for that patient (as listed in Table 4-3, column 6) were multiplied together. For example, a patient with the usual atrial arrangement (relative risk of 1.00), double inlet left ventricle (1.00) via two atrioventricular valves (1.00), discordant ventriculo-arterial connections (1.00) and pulmonary valvar or subvalvar stenosis (0.35); presenting at between 14 and 60 days of age (0.54), with balanced pulmonary blood flow (0.51) and after 1979 (1.00), had a product of relative risks of:

$$\mathbf{1.00 \times 1.00 \times 1.00 \times 1.00 \times 0.35 \times 0.54 \times 0.51 \times 1.00 = 0.096}$$

An estimated survival curve could then be created with this total relative risk using the method detailed in Appendix A (page 224). Seven examples of these estimated survival curves are illustrated in Figures 4.4 and 4.5. Patients A and B in Figure 4.4 illustrate the typical patients with a good risk, having the usual atrial arrangement, double inlet left ventricle, discordant ventriculo-arterial connections with pulmonary outflow restriction and either balanced (Figure 4.4, Curve A) or low (Figure 4.4, Curve B) pulmonary blood flow. These patients had predicted survival probabilities of 96% and 90% at age one year and 91% and 79% at age ten years, respectively. A similar patient, although with unobstructed and therefore high pulmonary blood flow (Figure 4.5, Curve E), had a considerably lower predicted survival of 79% at age one year and 60% at age ten years. Survival would be expected to be even lower in the presence of a common atrioventricular valve, as opposed to two separate atrioventricular valves, with

73% of such patients surviving to one year of age but only 30% of such patients predicted to reach ten years of age (Figure 4.5, Curve F).

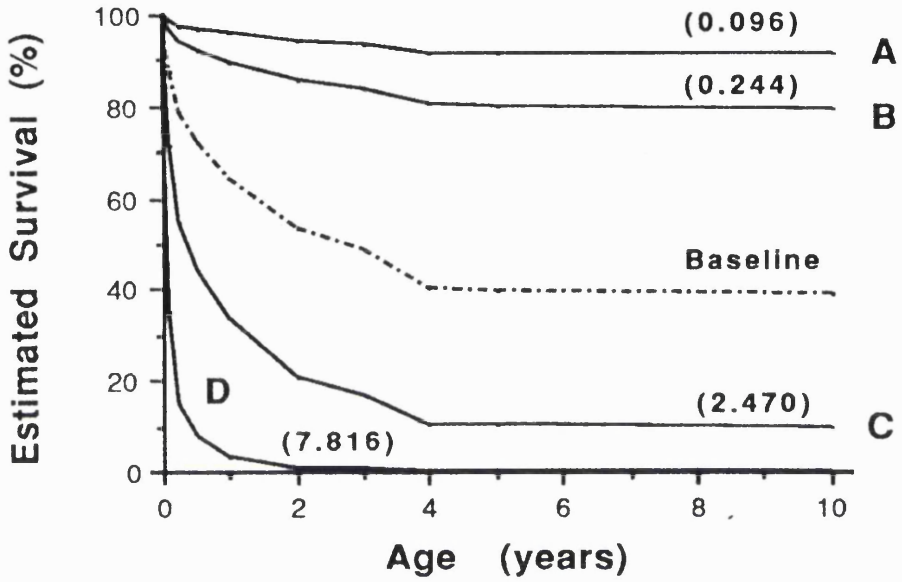

Figure 4.4. Estimated probability of survival curves before definitive surgery for patients with double inlet ventricle. **Curve A** refers to patients with the usual atrial arrangement, double inlet left ventricle, discordant ventriculo-arterial connections, and pulmonary valvar or subvalvar stenosis (or both), presenting between 14 and 60 days of age with balanced pulmonary blood flow. **Curve B** shows similar patients to Curve A, but presenting with low pulmonary blood flow; whilst **Curve C** represents those with the usual atrial arrangement, double inlet left ventricle and single outlet pulmonary atresia (aorta from either the dominant or rudimentary ventricle), presenting with low pulmonary blood flow at less than 14 days of age. **Curve D** corresponds to patients with right atrial isomerism, double inlet and double outlet right ventricle, a common atrioventricular valve, anomalous pulmonary venous connections, and low pulmonary blood flow, presenting at less than 14 days of age. The numbers in parentheses are the total calculated relative risks with respect to the hypothetical baseline patient (interrupted curve). Refer to the text for the predicted percentages of survival and to Appendix A for the methodology (page 224).

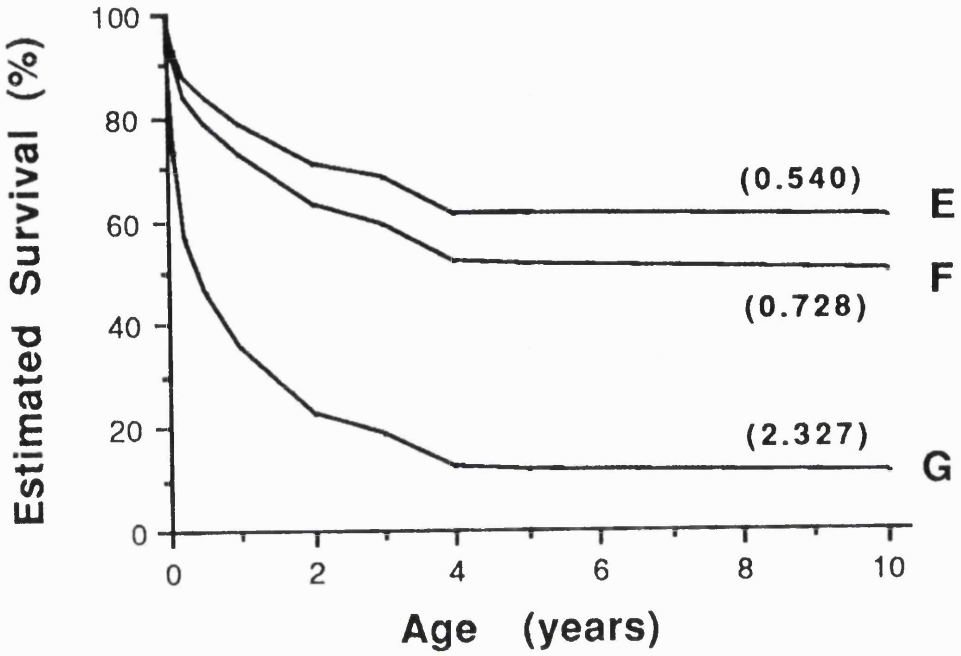

Figure 4.5. Estimated probability of survival curves before definitive surgery for patients with double inlet ventricle. **Curve E** refers to patients with the usual atrial arrangement, double inlet left ventricle, discordant ventriculo-arterial connections, and high pulmonary blood flow presenting between 14 and 60 days of age, whilst **Curve F** shows similar patients to Curve F, but with a common atrioventricular valve. **Curve G** represents patients with the usual atrial arrangement, double inlet left ventricle, discordant ventriculo-arterial connections, systemic outflow obstruction at any level and high pulmonary blood flow, presenting at less than 14 days of age. The numbers in parentheses are the total calculated relative risks with respect to the hypothetical baseline patient (interrupted curve in Figure 4.4). Refer to the text for the predicted percentages of survival and to Appendix A for the methodology (page 224).

The predicted outcome for patients presenting under 14 days of age, with the usual atrial arrangement, single outlet ventriculo-arterial connection with pulmonary atresia, and low pulmonary blood flow (Figure 4.4, Curve C) was even more pessimistic, with an expected survival of only 34% at age one year and 10% at age ten years. This was similar to that anticipated for a patient with the same anatomy as patient E but with additional systemic outflow obstruction at any level, with an estimated survival of only

36% at age one year and 11% at age ten years (Figure 4.5, Curve G). Predicted prognosis was worst in patients with the recognised complex association of right atrial isomerism, double inlet and double outlet right ventricle, a common atrioventricular valve, extracardiac totally anomalous pulmonary venous connections and reduced pulmonary blood flow, with only 3% of such patients expected to survive to one year of age and essentially none to reach age ten years (Figure 4.4, Curve D).

In addition, the relative risks detailed in Table 4-3 indicate that both severe acidosis and a very young age at presentation were particularly strong risk factors for mortality. These two categories correlated with the presence of severe associated lesions, such as systemic outflow obstruction at any level and totally anomalous pulmonary venous connections. Of note in this respect, is that the anomalous pulmonary venous return in most of the latter patients was severely obstructed.

Although the clinician could use this method to create predictive curves for other morphological and physiological combinations, for easier clinical use a simpler additive index for the different categories was created (Table 4-4). Table 4-5 was then constructed by retrospectively deriving the total scores for each of the 191 double inlet ventricle patients before cross tabulating these scores against actual patient outcome. Hence, the outcome for a new patient can be anticipated by adding together those category scores listed in Table 4-4 which pertain to the new patient, and thus to obtain a total score (those categories not listed having a score of zero). This total score can then be used to assess the patient's likely fate by examining the actual outcome of previous patients with a similar score, as detailed in the legend below Table 4-5.

Table 4-4. Additive index for the 191 patients with double inlet ventricle as calculated from the multivariate derived relative risks

	Rounded off Cox coefficient
Pulmonary valvar or subvalvar stenosis	-2
Presentation at age greater than two months	-2
Presentation at age two weeks to two months	-1
Balanced pulmonary blood flow	-1
Double inlet right ventricle	-1
Mirror image arrangement (situs inversus)	-1
Left atrial isomerism	-1
Right atrial isomerism	+1
Concordant ventriculo-arterial connections	+1
Pulmonary atresia	+1
Systemic outflow obstruction at any level	+1
Initial presentation prior to 1980	+1
Double outlet from the dominant ventricle	+2
Aortic atresia or common arterial trunk	+2
Anomalous pulmonary venous connections	+2
Presentation with low cardiac output and acidosis	+4

This index can be used to calculate a total score for patients with particular variants of double inlet ventricle at initial presentation. For example, the same patient used on page 91 would have a total score of -4: usual atrial arrangement (score of 0), double inlet left ventricle (0) with two atrioventricular valves (0), discordant ventriculo-arterial connections (0) and pulmonary valvar or subvalvar stenosis (-2), presenting at between age 14 and 60 days (-1) with balanced pulmonary blood flow (-1). The total score can now be used in comparison to the outcome of previous patients with a total score of -4, as shown in Table 4-5 overleaf, bearing in mind the reservations expressed there.

Table 4-5. Actual patient outcome versus multivariate derived additive index scores for the 191 patients with double inlet ventricle

Total additive risk score	Death before palliation			Death after palliation			Alive without operation			Alive after palliation			Definitive † surgery		
	N	%	median survival (years)	N	%	median survival (years)	N	%	median follow-up (years)	N	%	median follow-up (years)	N	%	median age at operation (years)
≤ 2 (N = 68)	3	4	0.3	10	15	1.1	10	15	8.3	21	31	7.1	24	35	6.3
- 1 (N = 27)	3	11	0.7	8	30	1.5	2	7	0.3	9	33	7.4	5	19	6.2
0-1 (N = 51)	12	24	0.3	25	49	0.8				5	10	10.0	9	18	5.8
2-3 (N = 18)	8	44	10 days	10	56	0.1									
≥ 4 (N = 27)	27	100	5 days												
Total (% 191)	**53**	**(28)**		**53**	**(28)**		**12**	**(6)**		**35**	**(18)**		**38**	**(20)**	

† Definitive surgery by means of a Fontan-type operation or ventricular septation procedure, exclusive of operative mortality.

This table allows assessment of the fate of new patients at initial presentation, by examining the outcome of previous patients with the same total score as the new patient, as derived from the additive index shown in Table 4-4. Thus, the patient used as an example on page 91 and the legend below Table 4-4 with a total score of - 4, would be expected to have a low chance of dying prior to (4%, with respect to similar patients) or after (15%) palliative surgery and would be likely to survive to an age when definitive surgery could be undertaken (15 + 31 + 35 = 91%).

Note: the index is only validated retrospectively. It may be expected therefore, that the true outcome for a new patient would be slightly more optimistic than that indicated by the observed proportions of past similar patients.

Such stratification of patients into risk groups can therefore be used to rapidly predict outcome in terms of survival with and without palliative surgery, but prior to definitive surgery, for infants with particular variants of double inlet ventricle. The predictive ability of this system was confirmed by its high correlation with the more complex multiplicative method ($r = 0.98$).

4.5 Effects of palliative surgery

Palliative operations were performed on 152 occasions for 121 out of the 191 patients (63%), as detailed in Table 4-6 and Figure 4.6. The median age at operation of the 57 patients who underwent construction of a systemic-to-pulmonary arterial shunt as their initial operation, was 3.4 months, with a range of one day to 77.6 months. The median age at surgery for the 35 children whose initial palliative procedure was isolated banding of the pulmonary trunk, was 5.4 months, with a range of 1.3 to 41.1 months. For the 18 patients who underwent banding of the pulmonary trunk together with aortic arch repair, the median age at surgery was 1.0 month, with a range of six days to 41.8 months.

Table 4-6. Types of operation undertaken for the patients with double inlet ventricle and their median ages at surgery (months)

	1st Operation		2nd Operation		
Operation type	**N**	**Med Age**	**N**	**Med Age**	**Total**
Systemic-to-pulmonary arterial shunt					
Blalock-Taussig †	49	4.6	19	37.6	68
BT and atrial septectomy †	1	8.2	1	29.5	2
Central interposition	7	2.0	4	66.6	11
Banding of the pulmonary trunk					
Isolated ± ligation of arterial duct	33	5.3	4	4.8	37
Banding & atrial septectomy	2	4.3	1	7.6	3
Aortic arch repair and banding of the pulmonary trunk					
Coarctation repair	17	0.9			17
Interrupted aortic arch repair	1	4.6			1
Isolated atrial septectomy	8	2.5			8
TAPVC repair	3	6.6			3
Grand Totals	**121**		**29**		**150**

† Operation was either a classical or modified (interposition) Blalock-Taussig shunt.

Two patients underwent a third palliative systemic-to-pulmonary arterial shunt at a median age of 44.7 months. Thus 152 palliative operations were performed for 121 out of the 191 patients (63%).

BT, Blalock-Taussig; Med, median; TAPVC, totally anomalous pulmonary venous connections.

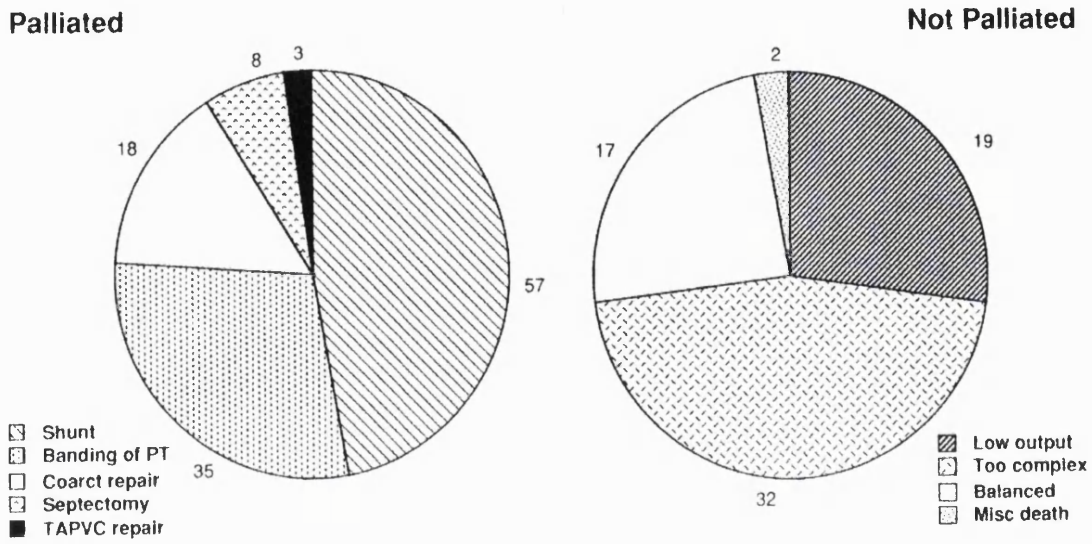

Figure 4.6. Initial management decisions for the 191 patients with double inlet ventricle. Palliative surgery was undertaken in 121 patients, whilst the remaining 70 patients received no palliation, for the reasons discussed in Section 4.6 (page 105).

Coarct repair, repair of coarctation of aorta or interrupted aortic arch together with banding of the pulmonary trunk; Misc, miscellaneous; PT, pulmonary trunk; Septectomy, atrial septectomy; Shunt, systemic-to-pulmonary arterial shunt; TAPVC, totally anomalous pulmonary venous connections.

The survival rates of the 57 patients for whom a systemic-to-pulmonary arterial shunt was constructed and the 35 patients who underwent isolated banding of the pulmonary trunk were comparable: 84% and 77% at age one year, 62% and 45% at age five years, and 51% and 45% at age ten years, respectively. In contrast, Figure 4.7 illustrates that the outcome of the 18 patients who required relief of aortic arch obstruction together with banding of the pulmonary trunk fared far worse, with only 44% and 22% surviving at ages one and five years, respectively ($p < 0.001$; log rank test).

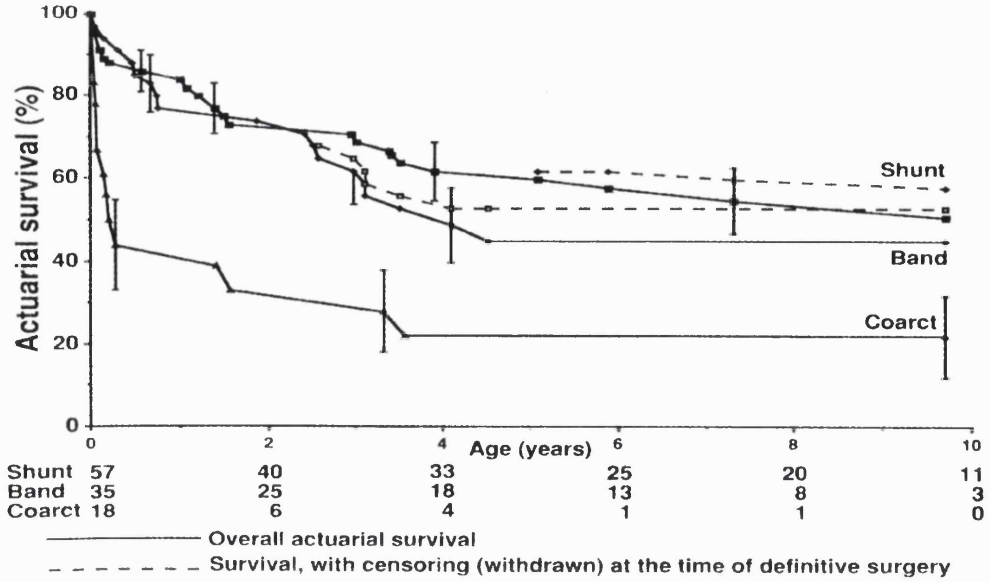

Figure 4.7. Actuarial survival curves of the patients with double inlet ventricle who underwent palliative intervention by construction of a systemic-to-pulmonary arterial shunt (57 patients - **Shunt**), by banding of the pulmonary trunk (35 patients - **Band**), and by repair of coarctation or interruption of the aortic arch together with banding of the pulmonary trunk (18 patients - **Coarct**). The interrupted curves refer to the survival of the patients before definitive surgery (i.e., the patients were 'censored' as alive at the time of definitive surgery - see Chapter 3, page 73). Patients who underwent relief of aortic arch obstruction had a significantly worse outcome ($p < 0.001$). The vertical bars are the actuarial 70% confidence limits and the numbers are the remaining patients for each group still being followed at that time, with reference to the time scale of the x-axis.

The calculated hazard rate prior to definitive surgery was two to four fold higher for the patients who underwent aortic arch surgery, than for the other two main palliated groups, although this dropped to a much lower level after one year of age (Figure 4.8). These hazard rates are numerated in Appendix Table B-1 (page 232).

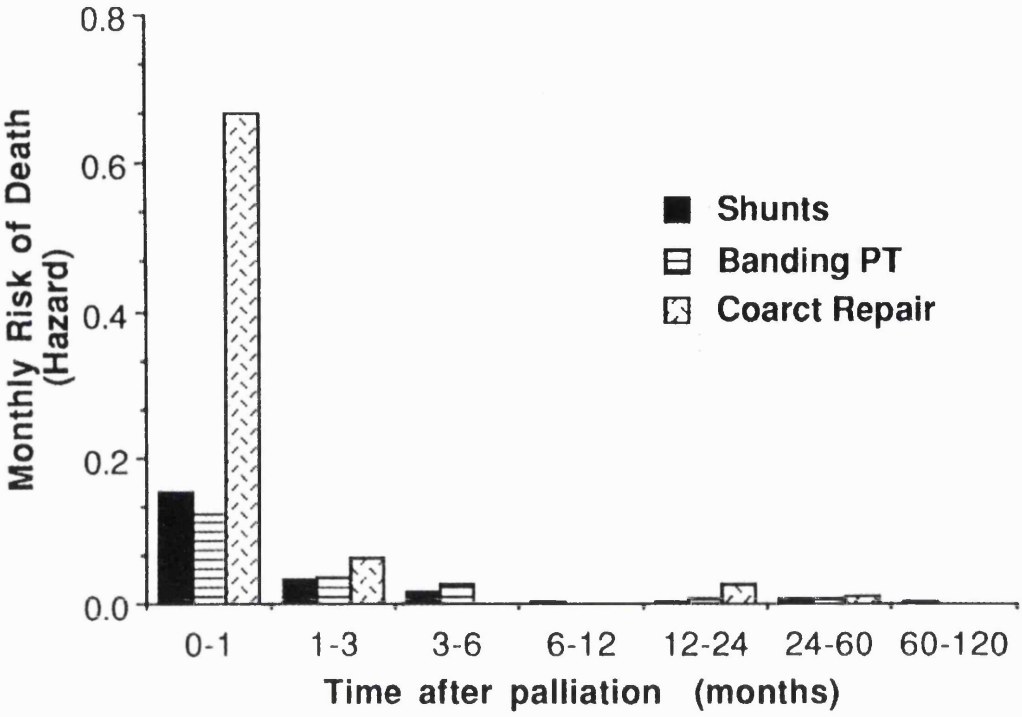

Figure 4.8. Histogram of the instantaneous monthly risk of death (hazard function) before definitive surgery for the patients with double inlet ventricle who underwent palliative intervention by construction of a systemic-to-pulmonary arterial shunt (57 patients - **Shunts**), by banding of the pulmonary trunk (35 patients - **Banding PT**), and by relief of coarctation or interruption of the aortic arch together with banding of the pulmonary trunk (18 patients - **Coarct repair**). There was a significantly higher risk for those who underwent repair of the aortic arch compared to that of the other groups during the first month, although subsequent hazards were not significantly different. The risks are numerated in Appendix Table B-1 (page 232).

Other initial palliative procedures included an isolated Blalock-Hanlon atrial septectomy in eight patients (Figure 4.6), at a median age of 10.4 weeks (range 6.0 - 240.6 weeks). Two patients died at this operation, whilst five others were known to be alive at over four years of age and one patient was lost to follow-up. Repair of extracardiac totally anomalous pulmonary venous connections was undertaken in three further infants, all with right atrial isomerism and a common atrioventricular valve, at ages 14, 28 and 50 weeks. None survived infancy.

4.5.1 Risk factor analysis incorporating palliative surgery factors

When the effects of palliative surgery were incorporated into the multivariate analysis, there was little change in the relative risks from the previous calculations (Appendix Table B-2, page 233). Correspondingly, only three minor changes resulted when recalculating the additive index (Table 4-7), indicating that the index was robust to the addition of these surgical factors.

The incorporation of the three time dependent covariates into this analysis allowed an assessment of the use of palliative surgery for infants with double inlet ventricle. Not surprisingly, there was a 6.5 fold higher relative risk of death for all patients who underwent these operations in the immediate post-operative time period, when compared to similar patients who did not undergo such treatment (Table 4-8). However, this risk had virtually 'normalised' by one month post-operatively and significant benefit was found when the analysis was repeated using the time period of over six months after intervention. This amounted to a one third less relative risk of death in the surviving surgically treated patients, when compared to patients who had not undergone such surgery.

Table 4-7. Additive index for the 191 patients with double inlet ventricle, calculated from the multivariate derived relative risks, including the risks of palliative surgery

	Rounded off Cox coefficient
Pulmonary valvar or subvalvar stenosis	-2
Presentation at age greater than two months	-2
Presentation at age two weeks to two months	-1
Balanced pulmonary blood flow	-1
Double inlet right ventricle	-1
Left atrial isomerism	-1
Mirror image arrangement (situs inversus)	-1
Right atrial isomerism	+1
Concordant ventriculo-arterial connections	+1
Pulmonary atresia	+1
Systemic outflow obstruction at any level	+1
Initial presentation prior to 1980	+1
Low pulmonary blood flow	+1
Double outlet from the dominant ventricle	+2
Anomalous pulmonary venous connections	+2
Aortic atresia or common arterial trunk	+3
Presentation with low cardiac output and acidosis	+5

This index can be used to calculate a total score for patients with particular variants of double inlet ventricle at initial presentation. For an example, see the legend below Table 4-4 (page 95).

Table 4-8. Relative risks of palliative surgery during different post-operative time periods for the patients with double inlet ventricle, after adjusting for the variables in Table 4-3

Post-operative time period	Overall (N = 121)	Systemic-to-pulmonary arterial shunt (N = 57)	Isolated banding of the pulmonary trunk (N = 35)	Banding of pulmonary trunk together with aortic arch repair (N = 18)
0 - 1 month	6.56 (3.60,11.90)	2.52 (1.05, 6.00)	20.00 (5.05,79.20)	16.92 (5.87,48.90)
1 - 6 months	1.84 (0.84, 4.01)	1.03 (0.36, 2.93)	5.49 (1.41,21.28)	1.25 (0.14,11.10)
Over 6 months	0.68 (0.28, 1.69)	0.43 (0.15, 1.24)	1.13 (0.29, 4.44)	0.91 (0.19, 4.27)

The numbers in parentheses indicate the 95% confidence limits.

This trend was also found when the three main palliative procedures were considered separately (Table 4-8). Those who underwent construction of a systemic-to-pulmonary arterial shunt received the most benefit from palliation in the medium term, with a relative risk of death which was less than half that of similar patients who had not undergone a shunt procedure. In contrast, those who required banding of the pulmonary trunk with or without additional relief of aortic arch obstruction, had a much higher risk of death in the first post-operative month. Although these patients did not show any apparent longer term benefit from palliation, their risks had 'normalised' when recalculated for the time period of over six months after their procedure.

4.6 Outcome of the patients who did not undergo palliative surgery

Over one third of the 191 patients with double inlet ventricle (70 patients, 37%) did not undergo a palliative operation during the whole follow-up period (Figure 4.6). Nineteen were neonates with irreversible low cardiac output at initial presentation to the tertiary centres (pH less than 7.20 for over six hours). All were considered to be unfit to withstand palliative surgery at the time of their assessment at the tertiary centres. Of relevance is that 17 of these patients presented in the pre-prostaglandin era. All died soon after first being seen.

In a further 32 infants with very complex combinations of lesions, surgery was not believed to offer any long term chance of definitive repair at the time of their initial presentation to the tertiary centres. The decision not to offer surgery was made on an arbitrary and individual basis in conjunction with the infants' parents. Table 4-9

compares the outcome of 28 of these patients with that of 22 infants, who were born with similar complex heart lesions but who *did* undergo a palliative operation. The two groups fared equally poorly with only three out of the 50 patients known to have survived to the end of the follow-up period.

In contrast, 17 children (9% of the whole group) with balanced physiology remained well without the use of palliative surgery throughout the period of study. Finally, two patients died prior to surgical intervention as neonates: one patient at catheterisation and one patient, a conjoined twin, died during the separation procedure.

4.7 Suitability for definitive surgery

4.7.1 Suitability for a Fontan-type operation at initial presentation

When first assessed in infancy at the tertiary centres, 136 (71%) of the 191 patients were considered by retrospective analysis to be potential candidates for a future Fontan-type procedure. A complex combination of lesions, which would have required multiple palliative procedures to achieve eventual Fontan suitability, was the most common reason for considering patients to be unsuitable for future definitive surgery *during the era of the study* (23 out of 55 patients, 42%). Table 4-9 details the anatomy of many of these cases. The two major single abnormalities which precluded a future Fontan-type operation were the presence of either subaortic stenosis, as found in 12 patients, or severe pulmonary arterial distortion, as found in nine patients (Table 4-10).

Table 4-9. Morphology and outcome of the patients with double inlet ventricle and complex associated lesions

	No surgical palliation	Palliated
Right atrial isomerism, common AV valve, pulmonary atresia, TAPVC	8	7
Coarctation, subaortic obstruction	4	6(1)
Right or left atrial isomerism, DIRV or DIIV, common AV valve, pulmonary atresia	3	3(1)
Left atrial isomerism, common AV valve, pulmonary atresia, TAPVC	3(1†)	2
Common AV valve, pulmonary atresia, pulmonary arterial distortion	4	3
Severe common AV valve regurgitation	2	1
Right atrial isomerism, common AV valve, subaortic obstruction	1	0
Interrupted aortic arch, pulmonary arterial distortion	1	0
Common arterial trunk, severe right AV valve regurgitation	1	0
Established pulmonary vascular disease	1(1)	0
	28(2)	**22(2)**

The numbers in parentheses indicate the number of patients who survived the follow-up period.

† This patient was lost to follow-up

AV, atrioventricular; DIIV, double inlet indeterminate ventricle; DIRV, double inlet right ventricle; TAPVC, totally anomalous pulmonary venous connections.

Table 4-10. Reasons why 55 out of the 191 patients with double inlet ventricle were deemed retrospectively to be unsuitable for a future Fontan-type procedure at initial presentation

Pulmonary arterial distortion	9
Subaortic stenosis: with aortic arch obstruction	8
isolated	2
with aortic valve stenosis	2
Aortic atresia	3
Severe common atrioventricular valve regurgitation	3
Complex anomalous systemic and pulmonary venous connections	3
Pulmonary vascular disease	1
Pulmonary venous atresia	1
Complex combination of lesions	23
Total	**55 (29%)**

4.7.2 Suitability for a ventricular septation procedure at initial presentation

In contrast, only 43 out of the 191 patients (23%) were considered retrospectively to have suitable morphologic characteristics for a future 'low risk' ventricular septation operation at initial presentation to the tertiary centres. The most common feature precluding suitability was a common atrioventricular orifice, whilst others included the presence of atrioventricular valve distortion and severe systemic or pulmonary outflow tract obstruction (Figure 4.9). None of the 55 patients considered unsuitable for a Fontan-type operation were deemed to be suitable for a ventricular septation procedure.

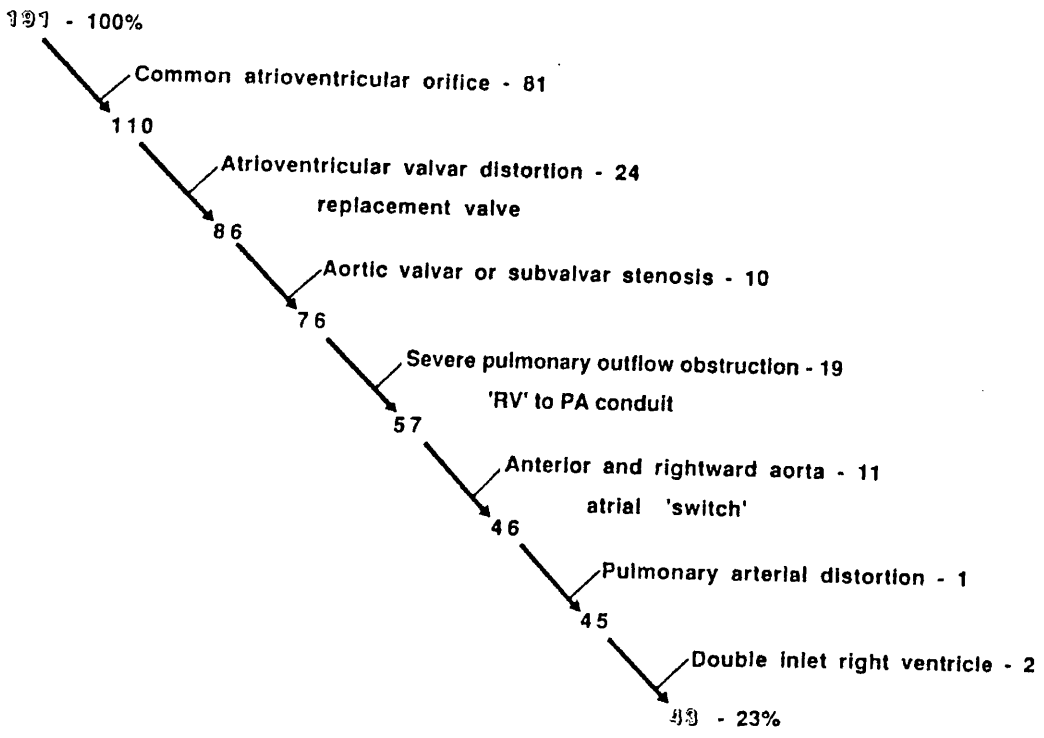

Figure 4.9. Flow chart of the 191 patients with double inlet ventricle illustrating the sequential 'drop out' of patients as the anatomic contraindications to a 'low-risk' ventricular septation operation, as found at initial assessment at the tertiary centres, were encountered. Only 23% of the patients had the required suitable morphologic features.

4.7.3 Actuarial survival with respect to suitability for definitive surgery

Actuarial survival of the above resultant patient groups was predictably better for the 136 patients (71%) potentially suitable for either definitive procedure (68% at age one year, 51% at age five years and 44% at age ten years), when compared to the remaining 55 patients considered to be unsuitable for both procedures, as illustrated in Figure 4.10, Curves B and D respectively ($p < 0.001$; log rank test). Only 45% of the latter 55 infants were still alive at one month of age and just 28% survived beyond one year. The 136 suitable patients were additionally stratified into the 93 infants who were

considered to be potentially suitable *only* for a Fontan-type procedure (Figure 4.10, Curve C - interrupted line) and 43 patients deemed to be suitable for both methods of definitive repair (Curve A). Of these two mutually exclusive groups, the latter fared the best: 80% versus 63% were alive at age one year, 60% versus 47% alive at age five years and 60% versus 37% surviving to age ten years, respectively ($p < 0.01$).

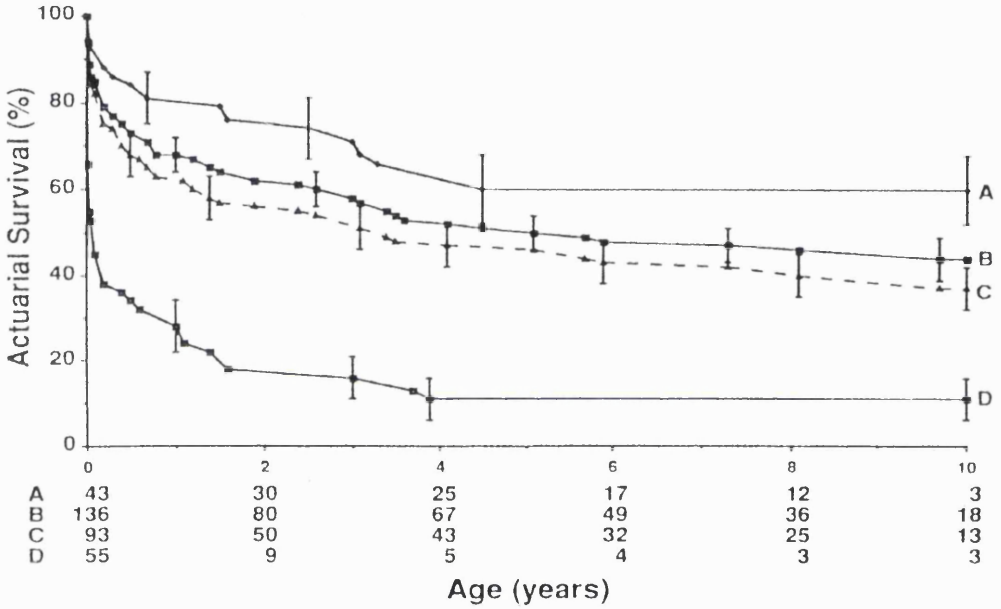

Figure 4.10. Kaplan-Meier actuarial survival curves of the 191 patients with double inlet ventricle with respect to their suitability for future definitive surgery at initial presentation: **Curve A**, the 43 patients considered to be potentially suitable for a ventricular septation operation (and also for a Fontan-type procedure); **Curve B**, the 136 patients considered to be potentially suitable for a Fontan-type procedure; and **Curve D**, the 55 patients considered to be unsuitable for either procedure. The interrupted **Curve C** refers to the 93 patients deemed to be solely suitable for a Fontan-type operation. The patients were withdrawn alive at the time of definitive surgery (see Chapter 3, page 73). The vertical bars are the actuarial 70% confidence limits and the numbers below the graph are the remaining patients still being followed at that time, with reference to the time scale of the x-axis. See the text for comparisons between the groups and the percentage survival details.

4.7.4 Outcome of the patients considered retrospectively to be suitable for a Fontan-type operation at initial presentation

Among these 136 patients, only 67% were known to be alive and without a new adverse feature at age one year and 57% at two years of age (Figure 4.11). The decrement continued, but more slowly thereafter.

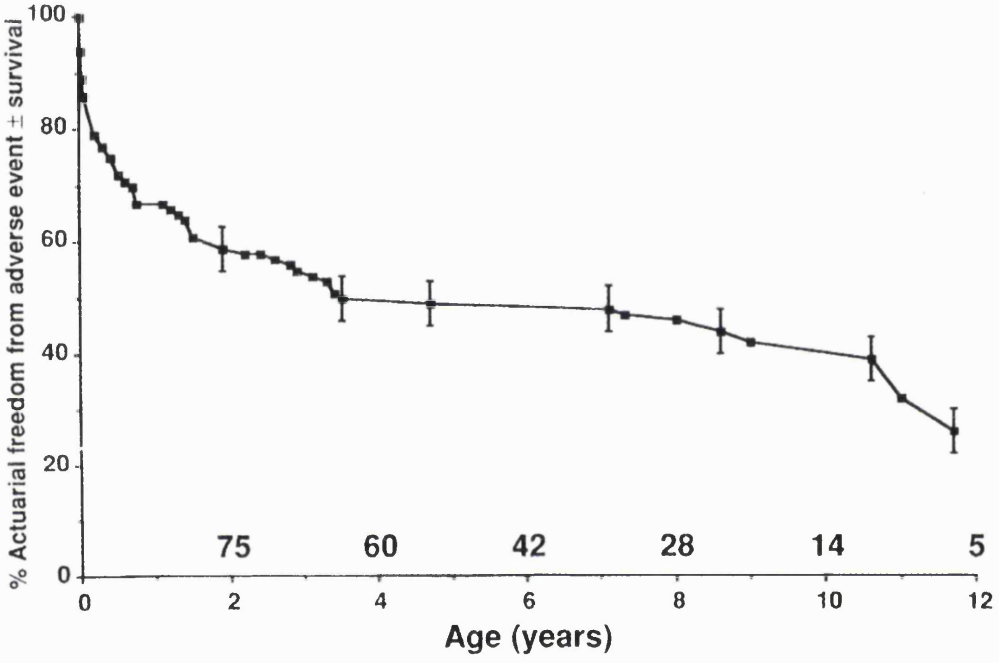

Figure 4.11. Actuarial survival curve free of adverse events (death or new adverse feature which would preclude a future Fontan-type operation) for the 136 patients with double inlet ventricle considered retrospectively to be suitable for such surgery at initial presentation. The patients were withdrawn alive at the time of definitive surgery (see Chapter 3, page 73). The vertical bars are the actuarial 70% confidence limits and the numbers are the remaining patients still being followed-up at the time, with reference to the time scale of the x-axis.

Death occurred most frequently either soon after the patient had presented in infancy to the tertiary centre with severe low cardiac output (19 patients, 14%) or after palliative surgery (22 patients, 16%), as detailed in Table 4-11. In addition, a further 14 patients (10%) died late and unexpectedly, 12 before four years of age (Figure 4.12).

Table 4-11. Reasons why the patients with double inlet ventricle died or ceased to be suitable for a Fontan-type procedure during follow-up (N = 136)

Death without known new adverse features	
Presentation with low cardiac output & acidosis	19
At palliative surgery:	
- Systemic-to-pulmonary arterial shunt	6
- Banding of the pulmonary trunk	7 (1)
- Banding of pulmonary trunk & coarctation repair	6
- Blalock-Hanlon atrial septectomy	2
Sudden and unexpectedly	14 (8)
Miscellaneous †	4 (1)
	58 (10)
New adverse features:	
Subaortic stenosis	7 (2)
Dominant ventricular dysfunction	3 (3)
Common atrioventricular valve regurgitation	3 (2)
Pulmonary vascular disease	5 (5)
	18 (12)
Total	**76 (22) = 56%**

The numbers in parentheses signify the patients in who died or in whom a new adverse feature first became evident after two years of age.

† Deaths were at catheterisation (two patients - one at three years of age), due to pneumonia (one patient) and during the separation procedure of conjoined twins (one patient).

Note: four of the 136 patients were lost to follow-up in infancy.

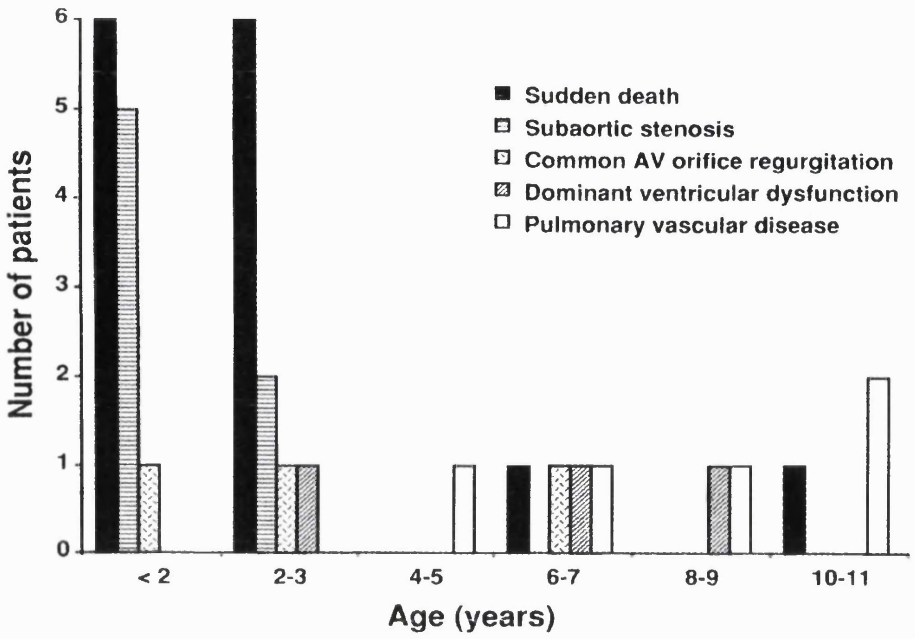

Figure 4.12. Bar chart showing the age at which sudden death occurred or when an adverse feature which precluded a Fontan-type operation first became evident, during follow-up period of the 136 patients with double inlet ventricle, considered retrospectively to be potential candidates for such future surgery at initial presentation.
AV, atrioventricular

Four new adverse features became evident in 18 patients (13%), with greatest prevalence in the first few years of life (Figure 4.12, Tables 4-11 and 4-12):

i) Subaortic stenosis became evident in seven patients, all by age 2.5 years. Three of these seven patients had previously undergone banding of the pulmonary trunk in isolation, whilst in the remaining four this operation was combined with the relief of aortic arch coarctation. Further details are given in Chapter 6 (page 156).

ii) Pulmonary vascular disease developed in five patients. They presented early in the study period and were asymptomatic, despite having high pulmonary blood flow on

retrospective review. Raised pulmonary arteriolar resistance was subsequently first documented at a mean age of 8.3 years. Two had received no palliation and two had only undergone an isolated atrial septectomy procedure. Consequently, all four went on to acquire irreversible pulmonary vascular disease but survived follow-up at ages ten to 15 years. A systemic-to-pulmonary arterial shunt was constructed for the fifth patient at age three years, but she eventually died at age ten years after an attempted modified Fontan procedure, two years after her raised pulmonary arteriolar resistance had first been diagnosed.

iii) Severe common atrioventricular valve regurgitation was first diagnosed in three patients at ages 1.5, 2.3 and 7.0 years. There was no similarity between their morphologic characteristics or the type of surgical palliation they each received. The two younger children died soon after diagnosis and the last was lost to follow-up at age eight years.

iv) Dominant ventricular dysfunction became evident in three patients, all of whom had double inlet left ventricle and discordant ventriculo-arterial connections. In two it was first diagnosed 1.6 and 6.0 years after banding of the pulmonary trunk, which was undertaken rather late at ages 1.3 and 3.0 years respectively. Both died soon after the complication was identified, one after an attempted total cavopulmonary connection. One further patient, who survived follow-up, developed ventricular dysfunction 6.4 years after the construction of a systemic-to-pulmonary arterial shunt when aged 1.1 years.

None of the patients developed new distortion of the pulmonary arteries that was sufficiently severe to preclude a Fontan-type operation. However, distortion to a degree that would require surgical attention did develop in 11 additional patients, eight after construction of systemic-to-pulmonary arterial shunt(s) and three after banding of the pulmonary trunk. Four of these eleven patients subsequently underwent a modified Fontan procedure with one death, whilst four were awaiting definitive surgery at the end of the follow-up period. Finally, three patients died suddenly at ages 3.5, 6.5 and 11.0 years.

4.7.4.1 Outcome with respect to management

Nine out of the 13 patients (69%) with balanced physiology (who had required no surgical palliation) and 25 out of the 42 patients (60%) who had undergone initial construction of a systemic-to-pulmonary arterial shunt, survived the follow-up period as suitable candidates for future definitive surgery. These outcomes were better than that of the 33 patients who had undergone initial palliation by banding of the pulmonary trunk alone, as only 14 of these 33 patients (42%) remained alive and suitable for future definitive surgery ($p < 0.05$). This excluded the eight potentially suitable patients lost to follow-up or yet to be recatheterised at the end of the period of study, as well as the 21 patients who died without receiving to palliative surgery, mostly due to their initial presentation to the tertiary centres with severe low cardiac output (Table 4-12).

Table 4-12. Detailed fate of the 136 patients with double inlet ventricle considered to be potentially suitable for a Fontan-type procedure at initial presentation

	No surgical palliation N = 38	Systemic-to-pulmonary arterial shunt N = 44	Isolated banding of the pulmonary trunk N = 34	Banding of pulmonary trunk and aortic arch repair N = 12	Atrial septectomy N = 8	Total 136
Death prior to definitive surgery without new adverse features:						
Presentation with low cardiac output	19 *					19
Sudden late death	2	5	6	1	0	14
At palliative surgery		6	7	6	2	21
Miscellaneous †	2 *	2				4
New adverse features precluding a Fontan-type procedure:						
Subaortic stenosis	0	0	3	4	0	7
Dominant ventricular dysfunction	0	1	2	0	0	3
Common atrioventricular valve regurgitation	0	2	1	0	0	3
Pulmonary vascular disease - isolated	2	1	0	0	2	5
Pulmonary arterial distortion not precluding a Fontan-type procedure ‡	0	8 ‡	2 ‡	1 ‡	0	11 ‡
Lost to follow-up	1	2	0	0	1	4
Awaiting recatheterisation at > 2 years of age	3	0	1	0	0	4
Suitable for a Fontan-type procedure at repeat catheterisation:						
Awaiting repair at end of follow-up period	4	11	7	1 #	0	23
Fontan procedure (operative death)	3(1)	8(3)	4(1)	0	3(1)	18
Total cavopulmonary connection	1	6	1	0	0	8
Ventricular septation (operative death)	1(1)	0	2(1)	0	0	3

* These 21 patients died prior to surgical intervention for the reasons stated. The remaining 17 out of 38 patients in this group had balanced physiology and electively received no palliation.

† Four deaths: two patients at catheterisation (one not palliated, one at three years of age); one patient due to pneumonia; and one patient at operative separation of conjoined twins (not palliated).

‡ These numbers are not included in the overall totals.

\# This was the only patient in this subgroup with concordant ventriculo-arterial connections and so not at risk of developing subaortic stenosis.

Those who required banding together with relief of aortic arch obstruction fared by far the worst, with only one of these 12 patients remaining alive and suitable for a Fontan-type operation at the end of the follow-up period ($p < 0.01$). This latter patient was the only one of this group with concordant ventriculo-arterial connections and was consequently not at risk of developing subaortic stenosis (see Chapter 6, page 156).

4.7.5 Outcome of the patients considered retrospectively to be suitable for a ventricular septation operation at initial presentation

Survival without a new adverse feature was greater in the 43 patients initially suitable for a ventricular septation procedure than in any other patient group, although only 70% remained alive at two years of age (Figure 4.13). The development of subaortic stenosis was the most prevalent serious adverse problem in these patients (Table 4-13, Figure 4.14). Although five patients became unsuitable for a ventricular septation procedure due to the development of marked pulmonary outflow tract obstruction at a mean age of 6.2 years (all of whom had mild subpulmonary obstruction at initial presentation), these five children remained suitable for a future Fontan-type operation.

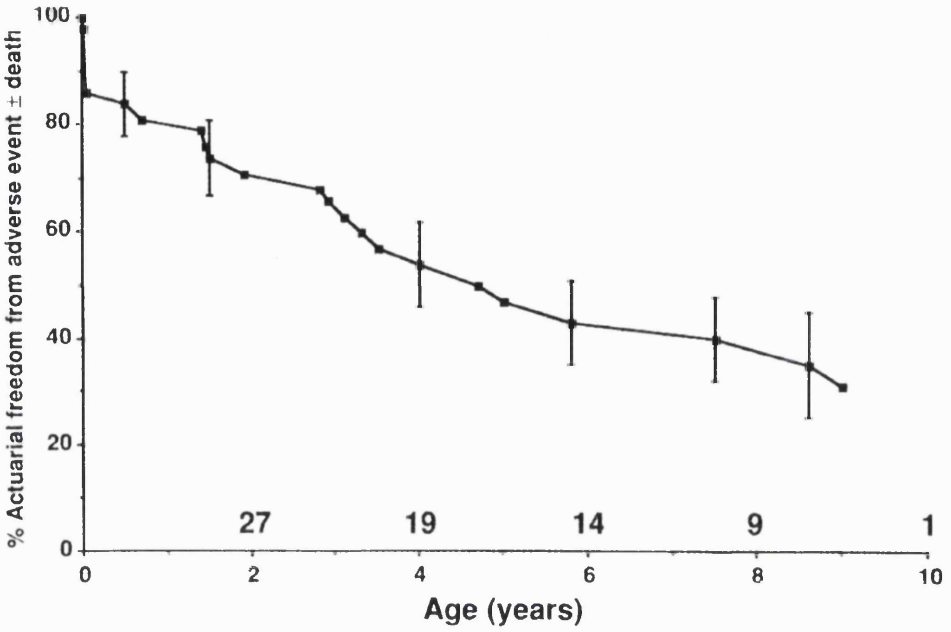

Figure 4.13. Actuarial survival curve free of adverse events (death or new adverse feature which would preclude a future ventricular septation operation) for the 43 patients with double inlet ventricle considered retrospectively to be suitable for such future surgery at initial presentation. The patients were withdrawn alive at the time of definitive surgery (see Chapter 3, page 73). The vertical bars are the actuarial 70% confidence limits and the numbers are the remaining patients still being followed at that time, with reference to the time scale of the x-axis.

Table 4-13. Reasons why the patients with double inlet ventricle died or ceased to be suitable for a ventricular septation operation during follow-up (N = 43)

Death without known new adverse features	
Low output presentation (pH < 7.20 for over 6 hours)	2
At palliative surgery:	
- Banding of pulmonary trunk	2 (1)
- Banding of pulmonary trunk & coarctation repair	2
Sudden and unexpectedly	3 (2)
Miscellaneous †	2
	11 (3)
New adverse features:	
Pulmonary outflow obstruction #	5 (5)
Subaortic stenosis	4
Dominant ventricular dysfunction	2 (2)
Pulmonary vascular disease	1 (1)
	12 (8)
Total	**23 (11) = 53%**

The numbers in parentheses signify the patients who died or in whom a new adverse feature first became evident after two years of age.

† Death at catheterisation (one patient) and during the operative separation of conjoined twins (one patient).

These patients remained suitable for a Fontan-type procedure.

Note: one of the 43 patients was lost to follow-up in infancy.

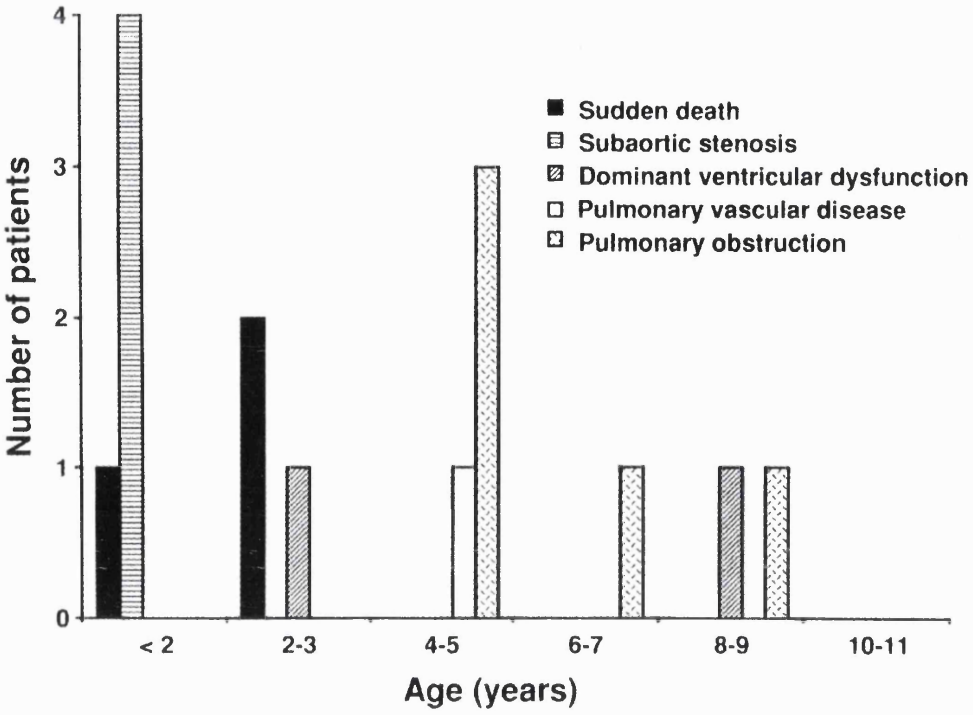

Figure 4.14. Bar chart showing the age at which sudden death occurred, or when an adverse feature which precluded a ventricular septation operation first became evident, during follow-up of the 43 patients with double inlet ventricle considered retrospectively to be potential candidates for such future surgery at initial presentation.

4.7.5.1 Outcome with respect to management

This was similar to the patients potentially suitable for a future Fontan-type operation, except that those who required no surgical palliation had a similar outcome to those who had undergone isolated banding of the pulmonary trunk: four out of eight patients (50%) compared to 11 out of 18 patients (61%) respectively, remained alive and suitable at the end of the follow-up period ($p > 0.1$). This was due to the development of severe pulmonary outflow tract obstruction in the infants with balanced pulmonary blood flow at initial presentation to the tertiary centres and who had

therefore not required early palliation (Table 4-14). A ventricular septation operation was chosen as the mode of definitive repair in only three out of the 16 suitable patients, with only one survivor. Seven other patients survived a Fontan-type procedure.

4.7.6 Outcome of the patients considered retrospectively to be unsuitable for definitive repair at initial presentation

Survival in this group was very poor (Figure 4.10, Curve D). An arbitrary decision was made not to embark on surgery in 32 out of 55 of these patients (Table 4-7), as detailed above. Only one of these infants, with early evidence of pulmonary vascular disease, survived into childhood. The other 23 patients were palliated, but there were 16 deaths in infancy (Table 4-15). Only one of the seven survivors became suitable for a Fontan-type procedure, after having undergone relief of subaortic stenosis by enlargement of a restrictive ventricular septal defect. The six other survivors remained alive but unsuitable during follow-up to a mean age of 10.2 years.

Table 4-14. Detailed fate of the 43 patients with double inlet ventricle considered to be potentially suitable for a ventricular septation operation at initial presentation

	No surgical palliation N = 15	Systemic-to-pulmonary arterial shunt N = 3	Isolated banding of the pulmonary trunk N = 19	Banding of pulmonary trunk and aortic arch repair N = 6	Total N = 43
Death prior to definitive surgery without new adverse features:					
Presentation with low cardiac output	2 *				2
Sudden late death	0	0	2	1	3
At palliative surgery		0	2	2	4
Miscellaneous †	2 *				2
New adverse features precluding a ventricular septation operation:					
Subaortic stenosis	0	0	1	3	4
Dominant ventricular dysfunction	0	0	2	0	2
Pulmonary outflow obstruction #	3	2	0	0	5
Pulmonary vascular disease - isolated	1	0	0	0	1
Lost to follow-up at under two years of age	1	0	0	0	1
Awaiting recatheterisation at > 2 years of age	2	0	1	0	3
Suitable for a ventricular septation operation at repeat catheterisation:					
Awaiting repair at end of the follow-up period	1	0	5	0	6
Ventricular septation procedure (operative death)	1(1)	0	2(1)	0	3
Modified Fontan procedure or Total cavopulmonary connection	2	1	4	0	7

* These four patients died prior to surgical intervention for the reasons stated. The remaining 11 out of 15 patients in this group had balanced physiology and electively received no palliation.

† One patient died at catheterisation and one patient died during the operative separation of conjoined twins.

\# These patients remained suitable for a Fontan-type procedure.

Table 4-15. Detailed fate of the 55 patients with double inlet ventricle considered to be unsuitable for either definitive operation at initial presentation

Reason for unsuitability	No surgical palliation N = 32	Systemic-to-pulmonary arterial shunt N = 13	Isolated banding of the pulmonary trunk N = 1	Banding of pulmonary trunk and aortic arch repair N = 6	Repair of TAPVC N = 3	Total N = 55
Subaortic stenosis ± aortic valve stenosis ± aortic arch obstruction	5	0	1 (1)	6 (1 †)	0	12
Aortic atresia	3					3
Pulmonary arterial distortion	5	3 (3)	0	0	1	9
Common atrioventricular valve regurgitation	2	1	0	0	0	3
Complex pulmonary and systemic venous drainage	1	2 (2)	0	0	0	3
Pulmonary vascular disease	1 (1)	0	0	0	0	1
Pulmonary vein atresia	1	0	0	0	0	1
Complex combination of lesions	**14**	**7**	**0**	**0**	**2**	**23**

The numbers in parentheses indicate the number of patients who survived the follow-up period in that subgroup.

† This patient was found to be suitable for a Fontan-type procedure when recatheterised at four years of age, after having undergone enlargement of a restrictive ventricular septal defect when aged four months.

TAPVC, totally anomalous pulmonary venous connections.

Chapter 5

Results of the 237 patients with tricuspid atresia

5.1 Morphology

In contrast to the patients with double inlet ventricle, only five of the 237 patients (2%) did not have the usual atrial arrangement (mirror image arrangement was present in four patients and right atrial isomerism in one patient). Equally, only a minority did not have a dominant left ventricle or concordant ventriculo-arterial connections (Table 5-1). All but 17 out of the 144 patients with concordant ventriculo-arterial connections had low or balanced pulmonary blood flow at initial presentation to the tertiary centres, due mostly to restriction at the level of the ventricular septal defect, although it was often at multiple levels (Table 5-2). This is in contrast to those with discordant ventriculo-arterial connections where all but eight out of the 58 patients had high pulmonary blood flow ($p < 0.001$). Of all the 75 patients with high pulmonary blood flow, 17 (23%) had mild pulmonary outflow obstruction at first presentation. Pulmonary arteries were deemed to be hypoplastic in 53% of those patients with 'effective' pulmonary atresia and in 44% of those with single outlet pulmonary atresia. Thirty two out of the 58 patients (55%) with discordant ventriculo-arterial connections had obstruction of the systemic outflow tract when first assessed, whilst this was not found in any of the patients with concordant ventriculo-arterial connections ($p < 0.0001$).

Table 5-1. Atrioventricular and ventriculo-arterial connections of the 237 patients with tricuspid atresia

	Morphology of Dominant Ventricle						
	Left (94%)		Right (3%)		Indeterminate (3%)	Total	
Nature of tricuspid valve atresia:	Absent	Imperforate	Absent	Imperforate	Absent	N	%
Ventriculo-arterial connections							
Concordant	137	7	0	0	-	144	61
Discordant	57†	0	1	0	-	58	24
Double outlet from the dominant ventricle	6	1‡	4	0	4	15	6
Double outlet from the rudimentary ventricle	4	0	0	0	-	4	2
Pulmonary atresia: aorta from the dominant ventricle	8	1	1	0	4	14	6
Pulmonary atresia: aorta from the rudimentary ventricle	0	1	0	0	0	1	0.5
Common arterial trunk	1	0	0	0	0	1	0.5
	213	**10**	**6**	**0**	**8**	**237**	**100**

† The rudimentary right ventricle was anterior and right sided in 50 out of 57 patients. It was anterior and left sided in the remaining seven patients.

‡ This patient had right atrial isomerism and an atrioventricular septal defect with partitioned orifices.

Table 5-2. Morphological and haemodynamic characteristics at initial presentation of the 237 patients with tricuspid atresia - I

	Ventriculo-arterial connections						
	Conc	**Disc**	**DODV**	**DORV**	**PAtr**	**Trunk**	**Total**
Number:	144	58	15	4	15†	1	237
Restriction to pulmonary blood flow							
At VSD alone	32	1‡	0	0	-	-	33
At VSD & RVOT	55	0	0	1	-	-	56
At RVOT alone	30	12	8	2	-	-	52
	117	**13**	**8**	**3**			**141**
Effective pulmonary atresia							
Intact ventricular septum	11	0	1	0	-	-	12
PV / PI atresia	4	0	2	0	-	-	6
	15	**0**	**3**	**0**			**18**
Pulmonary arterial abnormalities							
Hypoplastic PAs	23	0	3	1	9	0	36
Stenosis of PA	3	1	0	0	2	0	6
Absent PV syndrome	1	-	-	-	-	-	1
Systemic outflow tract obstruction							
Isolated coarctation of the aorta	0	11	1	0	0	1	13
Isolated interrupted aortic arch	0	3	1	0	0	0	4
Isolated subaortic stenosis	0	9	0	2	0	0	11
Aortic coarctation & subaortic stenosis	0	9	0	0	0	0	9
	0	**32**	**2**	**2**	**0**	**1**	**37**
Pulmonary blood flow							
Low	110	4	8	2	15†	0	139
High	17	50	5	2	0	1	75
Balanced	17	4	2	0	0	0	23

Table 5-2. Morphological and haemodynamic characteristics at initial presentation of the 237 patients with tricuspid atresia - II

	Ventriculo-arterial connections						
	Conc	**Disc**	**DODV**	**DORV**	**PAtr**	**Trunk**	**Total**
Number:	144	58	15	4	15†	1	237
Restrictive ASD	**30**	**14**	**2**	**1**	**3**	**0**	**50**
Left atrioventricular valvar abnormalities							
Straddling	2	2	2	0	0	0	6
Cleft	1	1	0	0	0	0	2
Stenosis	0	0	1	0	0	0	1
Regurgitation	0	1	0	0	0	0	1
	3	**4**	**3**	**0**	**0**	**0**	**10**
Miscellaneous lesions and abnormalities							
Left juxtaposition of atrial appendages	6	11	0	3	1†	0	21
Left superior caval vein	10	4	1	1	0	0	16
Anomalous PVC	3	0	1	0	0	0	4
Left ventricular diverticulum	1	0	0	0	1	0	2
Single coronary artery	0	2	0	0	0	0	2
Electrocardiographic findings							
Superior axis (<0°)	122	37	10	3	9	1	182
Mild left axis deviation (0-60°)	6	4	0	0	1	0	11
Normal (60-180°)	7	17	2	1	4	0	31
Lat T wave inversion	10	12	0	2	2	0	26
Complete heart block	1	2	0	0	0	0	3
WPW syndrome	0	0	1	0	1†	0	2
Unknown	9	0	3	0	1	0	13

† One patient in this group had single outlet pulmonary atresia with aorta from rudimentary ventricle.

‡ Patient with left atrioventricular valve to a dominant right ventricle, such that the ventricular septal defect restriction caused low pulmonary blood flow.

ASD, atrial septal defect; Conc, concordant; Disc, discordant; DODV, double outlet from the dominant ventricle; DORV, double outlet from the rudimentary ventricle; Lat, lateral; PAtr, pulmonary atresia; PAs, pulmonary arteries; PVC, pulmonary venous connections; PV, pulmonary valve; PV/PI, pulmonary valvar / pulmonary infundibular; RVOT, right ventricular outflow tract; Trunk, common arterial trunk; VSD, ventricular septal defect; WPW, Wolff-Parkinson-White.

The only significant gender effect found was that 63% of the 58 patients with tricuspid atresia and discordant ventriculo-arterial connections were male ($p < 0.05$).

5.2 Clinical presentation

As for double inlet ventricle patients, the mode of initial presentation to the tertiary centres was related to the pulmonary blood flow and the presence of associated lesions. Cyanosis was the presenting feature for 111 out of the 144 patients (77%) with concordant ventriculo-arterial connections, whereas 49 out of the 58 patients (85%) with discordant ventriculo-arterial connections presented with dominant signs of congestive heart failure ($p < 0.01$). The median age at presentation was similar in the 139 patients with low pulmonary blood flow (median age 16, range 1-236 days), the 75 infants with high flow (median age 32, range 1-236 days) and the 23 patients with balanced pulmonary blood flow (median age 36, range 1-364 days). The patients with balanced pulmonary blood flow were relatively asymptomatic when first seen. Additional severe acidosis (pH less than 7.20 for over six hours) was present in 13 neonates (6% of the total group) on arrival at the tertiary centres. Nine out of these 13 patients presented in the pre-prostaglandin era and all 13 had severe obstruction to either the systemic (six patients) or pulmonary (seven patients) outflow tract.

Only 50 out of the 237 patients (21%) were found to have a restrictive atrial communication at initial assessment with a further four patients (2%) developing this problem during follow-up. As a consequence, a transcatheter atrial septostomy was only undertaken for 26 patients using a balloon and three patients using a blade. All of these

procedures were undertaken during infancy. A further 16 patients underwent surgical atrial septectomy, either in isolation (two patients) or at the time of construction of a systemic-to-pulmonary arterial shunt (14 patients; see Section 5.4 below).

Electrocardiographic features were similar to those previously described by Dick and colleagues in 1975. Virtually all patients with concordant ventriculo-arterial connections had a superior QRS frontal axis, whilst this was a feature in only 37 out of the 58 patients (63%) with discordant ventriculo-arterial connections (Table 5-2). An interesting finding was that ST segment depression in the lateral chest leads was found in only ten out of the 135 patients (7%) with concordant ventriculo-arterial connections and available electrocardiograms, whilst it was apparent at initial assessment in 12 out of the 58 patients (21%) with discordant ventriculo-arterial connections ($p < 0.01$).

5.3 Overall survival

Overall survival of the 237 patients with tricuspid atresia was 72% at age one year, 53% at age five years and 46% at age ten years (Figure 5.1). When the 94 patients (40%) who underwent Fontan-type surgery were withdrawn ('censored') as alive at the time of this operation, survival was 56% at age five years and 49% at age ten years (Figure 5.1, upper curve). The hazard rate (monthly risk of death) prior to definitive surgery decreased dramatically over the first year of life, but persisted throughout the follow-up period (Figure 5.1, insert).

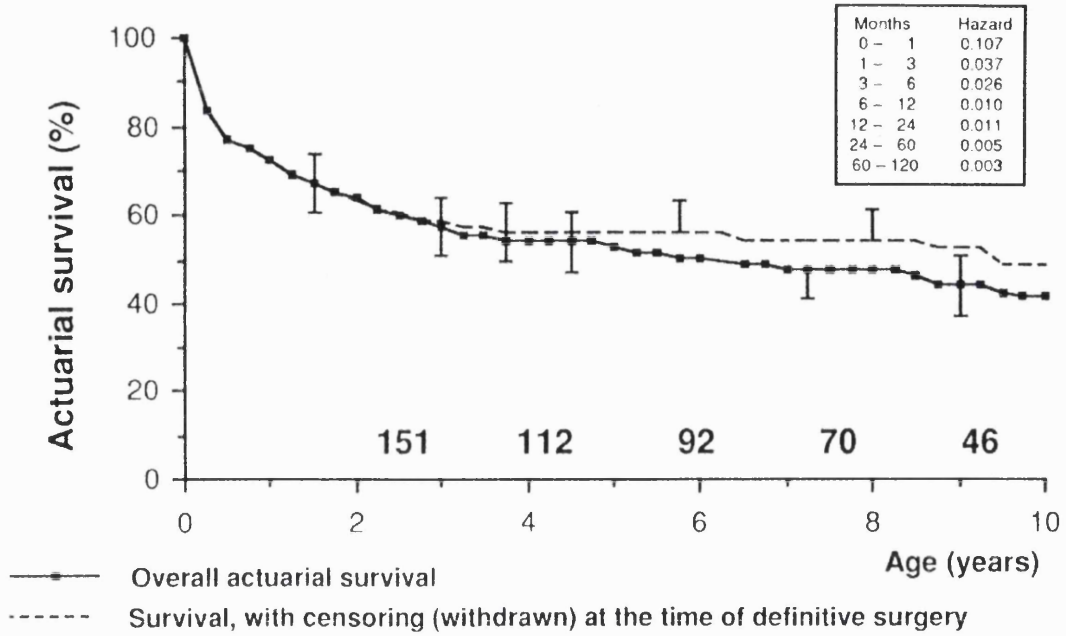

Figure 5.1. Kaplan-Meier actuarial survival curve of the 237 patients with tricuspid atresia. The upper interrupted curve refers to survival before definitive surgery (i.e., the patients were 'censored' as alive at the time of definitive surgery - see Chapter 3, page 73). The vertical bars are the actuarial 95% confidence limits, and the numbers are the remaining patients still being followed at that time, with reference to the time scale of the x-axis. The enclosed box gives the hazard functions for death as the instantaneous monthly risk of death during different age brackets.

Patients with tricuspid atresia and concordant ventriculo-arterial connections fared better than those with discordant connections, as illustrated in Figure 5.2: 81% versus 55% survival at age one year, 69% versus 36% at age five years and 58% versus 36% at age ten years, respectively ($p < 0.0001$). This can largely be explained by the high frequency of systemic outflow tract obstruction which occurred almost exclusively in the latter patients (Table 5-2) and whose outcome was relatively poor (see Chapter 6, page 156).

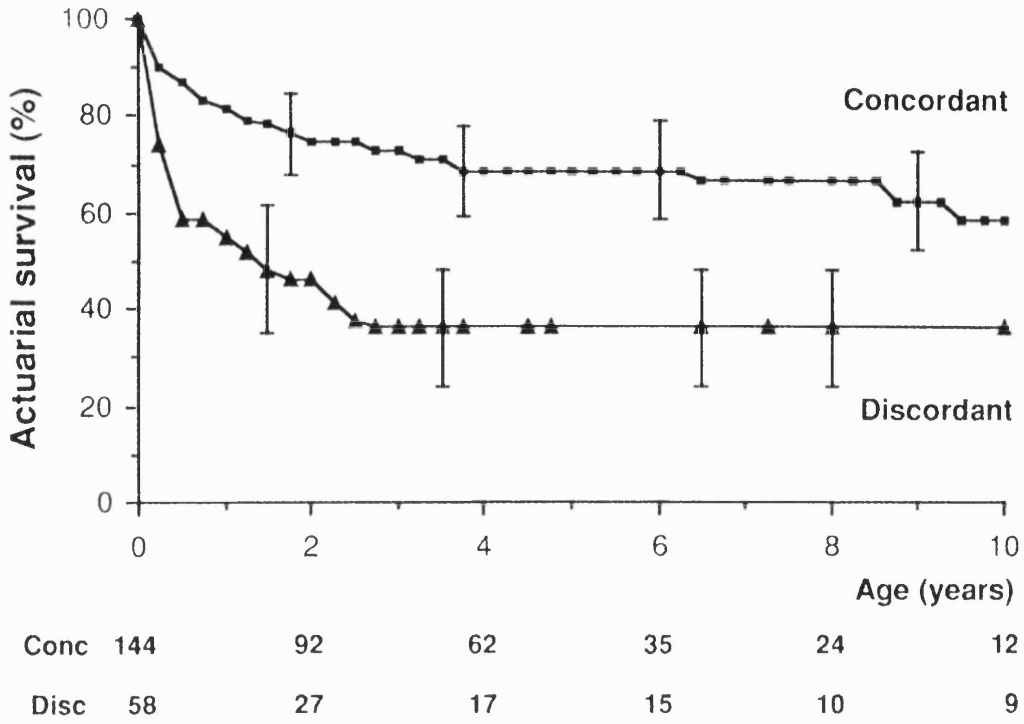

Figure 5.2. Kaplan-Meier actuarial survival curves which compare the outcomes before definitive surgery of the 144 patients with tricuspid atresia and concordant ventriculo-arterial connections (**Concordant**, **Conc**) with that of the 58 patients with tricuspid atresia and discordant ventriculo-arterial connections (**Discordant**, **Disc**). The latter had a significantly worse outcome ($p < 0.01$). The vertical bars are the actuarial 95% confidence limits, and the numbers below the graph are the remaining patients still being followed at that time, with reference to the time scale of the x-axis.

5.3 Risk factor analyses

For the purpose of the risk factor analyses, the 18 patients with *effective* pulmonary atresia (Table 5-2) were grouped together with the 15 patients with single outlet pulmonary atresia, as their haemodynamics were considered to be very similar. Consequently, the numbers of patients assigned to the categories of concordant and

double outlet from the dominant ventricle, ventriculo-arterial connections were proportionately reduced for these computations (Table 5-3).

Univariate risk factor analysis established that each of the following five categories had a relative risk of greater than two: discordant ventriculo-arterial connections, pulmonary atresia, subaortic stenosis, aortic arch obstruction, and severe acidosis at initial presentation. Thus, the monthly risk of mortality of each of these factors was at least twice that of the respective baseline category within each variable. In contrast, but similar to patients with double inlet ventricle, the presence of either pulmonary valvar or subvalvar stenosis, balanced pulmonary blood flow when first assessed, or an older age of initial presentation, each reduced the relative risk of death by at least a half, when compared to their respective baseline category within each variable (Table 5-3). These results are exemplified by the unadjusted actual percentage survival figures shown in Table 5-3 (column 2) for the patients who had a particular risk factor category within each variable, up to the time of definitive surgery.

Multivariate analysis established the outcome of the individual patient who inevitably presented with a combination of the variables listed in Table 5-3 and allowed the prediction of future patient outcome. As for patients with double inlet ventricle (Chapter 4, page 91), the first step in this process was to calculate the total relative risk of a patient with a particular variant of tricuspid atresia at initial presentation, by multiplying together the relative risks of the categories listed in Table 5-3 (column 6).

Table 5-3. Risk factor analysis for the 237 patients with tricuspid atresia, using factors as found at initial presentation - I

Variable and categories	N	%	Percentage Survival (mean ± SEM) at 2 years	at 5 years	Univariate relative risk (95% CL)	Multivariate relative risk (95% CL)
Ventriculo-arterial connections						
Concordant †	129	54	75 ± 4	68 ± 4	**p < 0.001**	**p < 0.001**
Discordant	58	24	46 ± 6	36 ± 6	2.69 (1.73, 4.19)	2.65 (1.25, 5.60)
Pulmonary atresia ‡	33	14	49 ± 9	43 ± 9	2.32 (1.36, 3.97)	1.59 (0.38, 6.69)
Double outlet dom ventricle	12	5	58 ± 14	58 ± 14	1.52 (0.60, 3.86)	2.27 (0.78, 6.55)
Double outlet rud ventricle	4	2	50 ± 2	50 ± 2	1.68 (0.41, 6.96)	0.29 (0.05, 1.71)
Common arterial trunk	1	1				
Interatrial communication						
Non-restrictive †	187	79	57 ± 4	53 ± 4	**p = 0.607**	**p = 0.403**
Restrictive	50	21	63 ± 7	60 ± 7	0.88 (0.53, 1.45)	0.80 (0.26, 3.41)
Pulmonary valvar and/or subvalvar obstruction						
Absent †	95	40	51 ± 5	45 ± 5	**p < 0.001**	**p = 0.931**
Present	142	60	71 ± 4	64 ± 4	0.52 (0.35, 0.76)	0.94 (0.26, 3.41)
Pulmonary arterial distortion						
Absent †	195	82	64 ± 3	57 ± 4	**p = 0.473**	**p = 0.841**
Present	42	18	61 ± 8	53 ± 8	1.19 (0.75, 1.91)	0.95 (0.55, 1.62)
Pulmonary blood flow at presentation						
Low †	139	59	62 ± 4	53 ± 4	**p = 0.002**	**p = 0.004**
High	75	32	57 ± 6	50 ± 6	1.15 (0.77, 1.72)	0.31 (0.10, 1.00)
Balanced	23	9	96 ± 4	91 ± 6	0.25 (0.09, 0.70)	0.21 (0.07, 0.62)

Table 5-3. Risk factor analysis for the 237 patients with tricuspid atresia, using factors as found at initial presentation - II

Variable and categories	N	%	Percentage Survival (mean ± SEM) at 2 years	at 5 years	Univariate relative (95% CL)	Multivariate relative (95% CL)
Subaortic stenosis						
Absent †	217	92	67 ± 3	60 ± 3	**p < 0.001**	**p < 0.001**
Present	20	8	20 ± 9	15 ± 8	4.17 (2.46, 7.07)	5.42 (2.05,14.36)
Aortic arch obstruction						
Absent †	220	93	65 ± 3	59 ± 3	**p < 0.001**	**p = 0.002**
Present	17	7	35 ± 12	22 ± 10	2.92 (1.66, 5.14)	4.34 (1.72,10.99)
Severe acidosis at presentation						
No acidosis †	224	95	66 ± 3	59 ± 3	**p < 0.001**	**p < 0.001**
Acidosis present	13	5	8 ± 7	0	8.57 (4.61,15.93)	7.23 (3.33,15.74)
Age at initial presentation						
Less than two weeks of age †	99	42	52 ± 5	44 ± 5	**p < 0.001**	**p = 0.001**
Two weeks - two months of age	60	25	68 ± 6	61 ± 6	0.58 (0.36, 0.93)	0.64 (0.38, 1.08)
After two months of age	78	33	74 ± 5	69 ± 5	0.42 (0.26, 0.68)	0.43 (0.25, 0.71)
Era of initial presentation						
After 1979 †	108	46	62 ± 5	55 ± 5	**p = 0.907**	**p = 0.411**
Prior to 1980	129	54	64 ± 4	57 ± 4	0.98 (0.66, 1.45)	1.20 (0.78, 1.84)

† Baseline category. CL, confidence limits; dom, dominant; rud, rudimentary; SEM, standard error of the mean.

‡ The pulmonary atresia category includes the 18 patients with 'effective' pulmonary atresia, as detailed in Table 5-2 and explained in the text on page 131.

To calculate the total relative risk of a patient with a particular variant of tricuspid atresia at presentation, all the relative risks for that patient are multiplied together. See page 135 for an example. An estimated survival curve can then be produced using the methodology detailed in Appendix A (page 224).

For example, a patient with concordant ventriculo-arterial connections (relative risk of 1.00) and pulmonary valvar or subvalvar stenosis (0.94), presenting at an age of over 60 days (0.64), with balanced pulmonary blood flow (0.21) and all other categories at their baseline values (i.e., a relative risk of 1.00 and thus will not alter the computations), had a product of relative risks of:

$$\mathbf{1.00 \times 0.94 \times 0.64 \times 0.21 = 0.126}$$

An estimated survival curve could then be generated using this total relative risk by means of the method described in Appendix A (page 224). Hypothetical curves were created to illustrate the anticipated fate of patients with various common variants of tricuspid atresia, as illustrated in Figures 5.3 and 5.4.

The most favourable estimated outcomes were for patients with concordant ventriculo-arterial connections, regardless of pulmonary blood flow (Figure 5.3, Curves A and B), with five year predicted survival probabilities of around 90%. The anticipated outlook for those with pulmonary atresia (Figure 5.3, Curve C) or discordant ventriculo-arterial connections (Figure 5.4, Curves D and E) was considerably worse, with five year estimated survivals of only 40% to 75%.

Although the morphological variants in the patients with tricuspid atresia were far fewer than those of the double inlet ventricle cohort, the forecast outlook for patients with aortic arch obstruction was equally poor, the predicted five year survival being only 15% (Figure 5.4, Curve F).

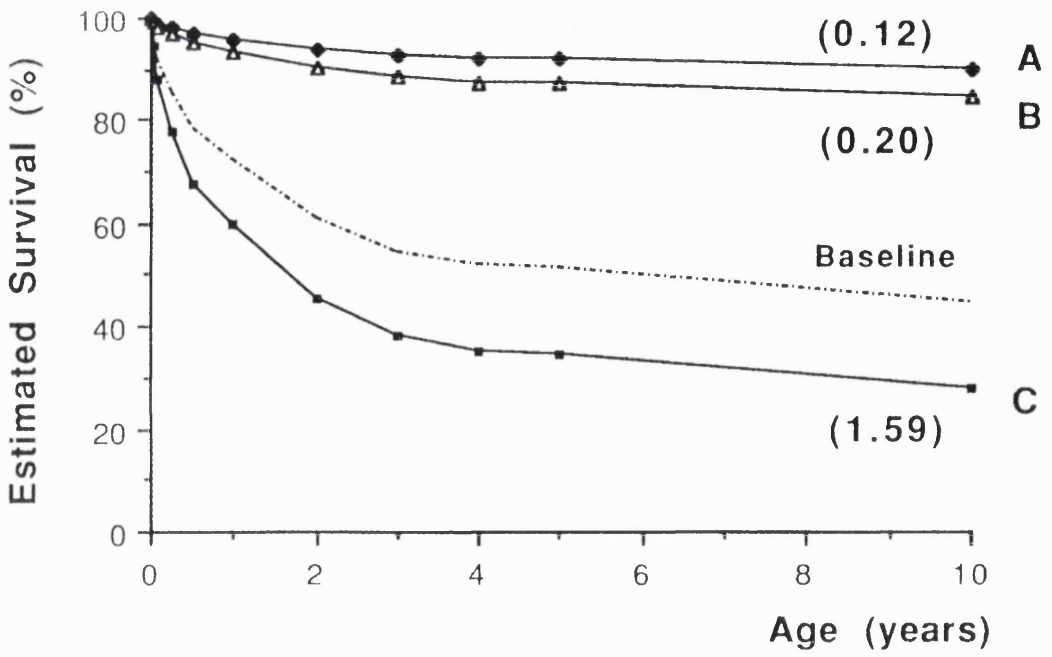

Figure 5.3. Estimated probability of survival curves before definitive surgery for patients with tricuspid atresia. **Curve A** shows those with concordant ventriculo-arterial connections, pulmonary valvar and / or subvalvar stenosis and balanced pulmonary blood flow, presenting at less than 60 days of age. **Curve B** shows similar patients but without pulmonary stenosis and therefore high pulmonary blood flow, presenting between 14 and 60 days of age; whilst **Curve C** represents those with pulmonary atresia (both effective and single outlet), presenting with low pulmonary blood flow at less than 14 days of age. The numbers in parentheses are the total calculated relative risks with respect to the hypothetical baseline patient (interrupted curve). Refer to the text for the predicted percentages of survival and to Appendix A for the methodology (page 224).

As for patients with double inlet ventricle, a simpler additive risk index was calculated (Table 5-4) and cross tabulated against the retrospectively derived, actual outcome of the 237 patients with tricuspid atresia (Table 5-5). This allowed the prediction of outcome before definitive surgery for future patients by relating the total additive score of the new individual to the outcome of previous patients with a similar score (see the

legend below Table 5-5 and Chapter 4, page 94). As before, those categories not listed had a score of zero and there was a high correlation between the logarithms of the relative risks for the index and the more precise multiplicative method (r = 0.98).

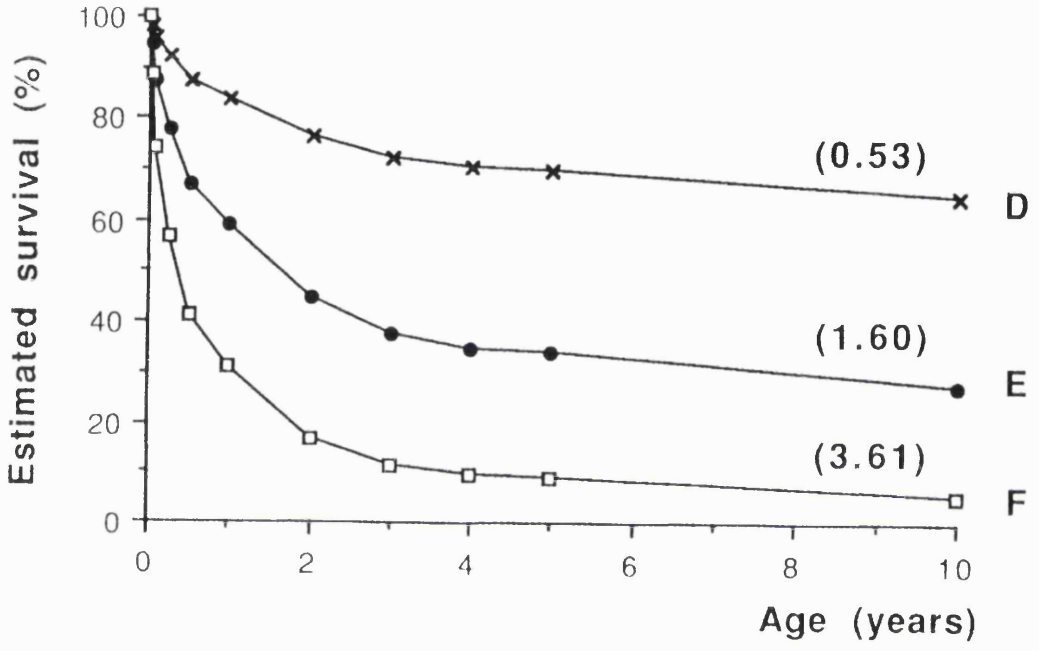

Figure 5.4. Estimated probability of survival curves before definitive surgery for patients with tricuspid atresia and discordant ventriculo-arterial connections. **Curve D** shows those presenting with high pulmonary blood flow between 14 and 60 days of age; whilst **Curve E** shows similar patients but with pulmonary valvar and/or subvalvar stenosis and low pulmonary blood flow, presenting between the same ages. **Curve F** represents similar patients to Curve D but with additional aortic arch obstruction, presenting at less than 14 days of age. The numbers in parentheses are the total calculated relative risks with respect to the hypothetical baseline patient (interrupted curve in Figure 5.3). Refer to the text for the predicted percentages of survival and to Appendix A for the methodology (page 224).

Table 5-4. Additive index for all 237 patients with tricuspid atresia and for the 204 potentially suitable patients for a Fontan-type operation at initial presentation, as calculated from the multivariate derived relative risks

	Rounded off Cox coefficient	
	N=237	N=204
Balanced pulmonary blood flow	-2	-3
High pulmonary blood flow	-2	-1
Double outlet from the rudimentary ventricle	-2	0
Presentation at age greater than two months	-1	-1
Presentation at age two weeks to two months	-1	0
Discordant ventriculo-arterial connections	+1	+1
Pulmonary atresia (single outlet or 'effective')	+1	+1
Double outlet from the dominant ventricle	+1	0
Aortic arch obstruction	+2	+3
Subaortic stenosis	+2	+2
Presentation with severe low cardiac output and acidosis	+3	+3

This index is used to calculate a total score for patients with particular variants of tricuspid atresia at the time of first assessment. For example, the patient used on page 135 would have a total score of -3 (or -4): concordant ventriculo-arterial connections (score of 0) and pulmonary valvar or subvalvar stenosis (0), presenting after 60 days of age (-1) with balanced pulmonary blood flow (-2 or -3). The total score can now be used in comparison to the outcome of previous patients with a total score of -3 (or -4), as shown in Tables 5-5 (overleaf) and 5-10 (page 155), bearing in mind the reservations expressed there.

Table 5-5. Actual patient outcome versus multivariate derived additive index scores for the 237 patients with tricuspid atresia

Total additive risk score	Death before palliation			Death after palliation			Alive without operation			Alive after palliation			Definitive † surgery		
	N	%	median survival (years)	N	%	median survival (years)	N	%	median follow-up (years)	N	%	median follow-up (years)	N	%	median follow-up (years)
≤ 3 (N = 24)							1	4	17.4	3	13	4.5	20	83	5.0
- 2 (N = 33)	2	6	8.1	6	18	1.1	2	6	13.9	4	12	9.9	19	58	4.8
- 1 (N = 68)	3	4	1.0	25	37	1.1	1	2	1.2	6	9	6.2	33	48	4.8
0 (N = 61)	9	15	0.3	25	41	1.1	2	3	7.1	11	18	7.4	14	23	3.6
+ 1 (N = 41)	8	19	0.1	19	47	0.2				6	15	8.2	8	19	3.9
≥ 2 (N = 10)	6	60	3 days	4	40	0.1									
Total (% 237)	**28**	**(12)**		**79**	**(33)**		**6**	**(2)**		**30**	**(13)**		**94**	**(40)**	

† Signifies definitive surgery by means of a Fontan-type operation, exclusive of operative mortality.

This table allows assessment of the fate of new patients at initial presentation, by examining the outcome of previous patients who had the same total score as the new patient, as derived from the additive index shown in Table 5-4, column 1. Thus, the patient used as an example on page 135 and the legend below Table 5-4 with a total score of -3, would be expected to have a very low chance of dying prior to or after palliative surgery and would be very likely to survive to an age when definitive surgery could be undertaken (4 + 13 + 83 = 100% in comparison to other patients).

Note: the index is only validated retrospectively. It may be expected therefore, that the true outcome for a new patient would be slightly more optimistic than that indicated by the observed proportions of past similar patients.

5.5 Survival after palliative surgery

Palliative surgery was performed on 253 occasions for 194 of the 237 patients (82%), as detailed in Table 5-6. The median age at surgery of the 135 patients who underwent construction of a systemic-to-pulmonary arterial shunt as their first operation, was two months, with an age range of one day to 61.1 months. The median age at surgery of the 32 patients who underwent an initial isolated banding of the pulmonary trunk procedure was 3.8 months, with an age range of 15 days to 64.6 months. The median age at operation for the 17 patients who underwent banding of the pulmonary trunk together with aortic arch repair was 12 days, with an age range of three days to 4.4 months. Successive systemic-to-pulmonary arterial shunts were constructed for 39 patients.

Not surprisingly, given the high proportion of infants with tricuspid atresia who presented with low pulmonary flow, nearly twice as many patients with tricuspid atresia required construction of a systemic-to-pulmonary arterial shunt as initial palliation, compared to those with double inlet ventricle: 135 out of 237 patients (57%) compared to 57 out of 191 patients (30%), respectively ($p < 0.01$). Survival after operation for these 135 patients was similar to that of the 31 patients who underwent isolated banding of the pulmonary trunk: 76% versus 87% at age one year, 56% versus 62% at age five years and 47% versus 48% at age ten years, respectively (Figure 5.5).

Table 5-6. Types of operation undertaken for patients with tricuspid atresia and their median ages at surgery (months) - I

Operation	1st Operation N	1st Operation Med Age	2nd Operation N	2nd Operation Med Age	Total
Systemic-to-pulmonary arterial shunt					
Classical Blalock-Taussig shunt					
Right	28 (2)	3.7			28
Left	3	5.3	3	18.5	6
Interposition (modified) Blalock-Taussig shunt					
Right	37 (1)	0.7	6	22.4	43
Left	33	2.6	25	26.8	58
Right & atrial septectomy	10 (3)	4.1			10
Central interposition shunt	3	0.2	3	50.1	6
and WPW tract ablation			1	66.4	1
Waterston shunt (Ao to right PA anastomosis)	18 (4)	1.5	4 (1)	3.1	22
and atrial septectomy			1	17.9	1
Potts shunt (descending Ao to left PA anastomosis)	1 (1)	1.4			1
Infiltration of the arterial duct	2	0.1			2
Total	**135**		**43**		**178**
Banding of the pulmonary trunk					
Isolated ± ligation of the arterial duct	28 (3)	3.8	1	34.5	29
and atrial septectomy	3	4.6			3
Total	**31**		**1**		**32**
Aortic arch repair together with banding of the pulmonary trunk					
Coarctation repair	15 (8)	0.5			15
Interrupted aortic arch repair	2	0.4			2
Aortic arch reconstruction			1	0.7	1
Total	**17**		**1**		**18**

Table 5-6. Types of operation undertaken for patients with tricuspid atresia and their median ages at surgery (months) - II

	1st Operation		2nd Operation		
Operation	**N**	**Med Age**	**N**	**Med Age**	**Total**
Other miscellaneous palliative procedures					
Isolated atrial septectomy			2 (1)	14.4	2
Classical Glenn shunt	5 (1)	8.1			5
TAPVC repair	1 (1)	102.8			1
Enlargement RV outflow tract	1	20.6	1	25.7	2
Banding of left & right PAs for interrupted aortic arch	1	9.8			1
Mitral valve repair & banding of the pulmonary trunk	1	105.1			1
Operations for subaortic stenosis					
DKS anastomosis & SPA shunt	2 (2)	13.3	2 (1)	14.0	4
Left ventricle to aorta conduit and atrial septectomy			1 (1)	17.5	1
Enlargement of RV outflow tract			1	18.1	1
Modified Fontan & DKS anastomosis			3 (3)	16.7	3
Modified Fontan & enlargement of VSD ± RV outflow tract			2	61.7	2
Definitive surgery without the presence of subaortic stenosis					
Fontan-type operation	9	50.5	63 (18)	53.1	72
Grand Totals	**203**		**120**		**323**

The numbers in parentheses are the number of operative (in hospital) deaths.

Seven patients went on to a third palliative procedure: central interposition SPA shunt (four patients, all with severe pulmonary arterial distortion), left interposition SPA shunt (one patient), banding of the pulmonary trunk (one patient, after a classical Glenn procedure), and repair of TAPVC (one patient). There were no operative deaths.

A further 21 patients underwent a Fontan-type procedure as their third operation at a median age of 83.9 months with two operative deaths, whilst one patient died at his fourth operation at age 102.3 months. There were a total of 94 Fontan-type operations - see also Table 5-8.

Ao, aorta; DKS, Damus-Kaye-Stansel (anastomosis of aorta to proximal pulmonary artery); Med, median; PA, pulmonary artery; RV, right ventricular; SPA, systemic-to-pulmonary arterial; TAPVC, totally anomalous pulmonary venous connections; VSD, ventricular septal defect; WPW, Wolff-Parkinson-White.

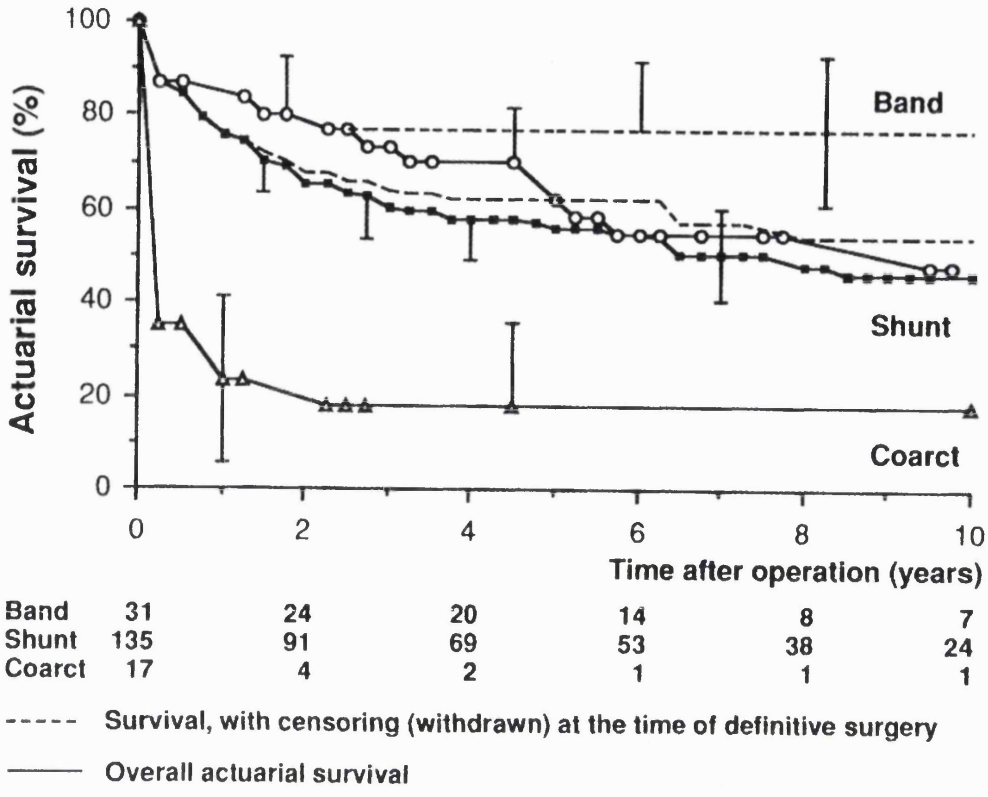

Figure 5.5. Actuarial survival curves of the patients with tricuspid atresia who underwent initial palliation either by construction of a systemic-to-pulmonary arterial shunt (135 patients - **Shunt**); by isolated banding of pulmonary trunk (31 patients - **Band**); or by relief of aortic arch obstruction together with banding of the pulmonary trunk (17 patients - **Coarct**). The interrupted curves refer to the survival of the patients before definitive surgery (see Chapter 3, page 73). Patients who underwent relief of aortic arch obstruction had a significantly worse outcome ($p < 0.001$). The vertical bars are the actuarial 95% confidence limits, and the numbers are the remaining patients for each group still being followed at that time, with reference to the time scale of the x-axis.

Operative mortality was lower for the patients who had undergone Blalock-Taussig shunt procedures than for those in whom other surgical methods had been used to augment pulmonary blood flow: 6 out of 111 patients (5%) compared to 8 out of 24 patients (32%), respectively ($p < 0.01$). Actuarial survival was much worse for the latter group (Figure 5.6).

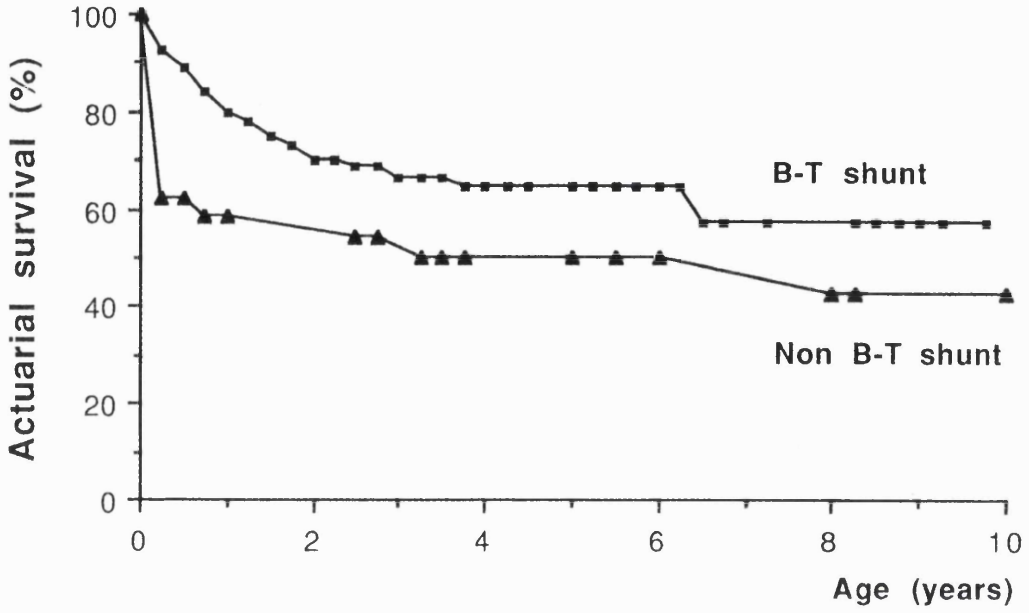

Figure 5.6 . Actuarial survival curves which compare the outcome of the 111 patients who underwent construction of a systemic-to-pulmonary arterial shunt as initial palliation by means of a Blalock-Taussig procedure (**B-T shunt**), with the 24 patients whose pulmonary blood flow was augmented using other surgical techniques (**Non B-T shunt**). The former had a significantly better short and long term outcome ($p < 0.01$).

Survival was similar for the 12 patients with concordant and the 15 patients with discordant ventriculo-arterial connections after they had undergone isolated banding of the pulmonary trunk (83% versus 87% at age one year and 83% versus 67% at ages five and ten years, respectively). Again, similar to the patients with double inlet ventricle, the fate of the 17 patients who underwent banding of the pulmonary trunk together with relief of aortic arch obstruction was dismal, with only 23% survival at age one year and 18% survival at five years of age (Figure 5.5; $p < 0.001$, log rank test). Correspondingly, the initial calculated hazard rates (instantaneous monthly risk of

death) for the 183 patients who underwent the three main palliative operations (prior to definitive surgery) were four times higher in those requiring aortic arch surgery, than for those who underwent either construction of a systemic-to-pulmonary arterial shunt or isolated banding of the pulmonary trunk (Table 5-7). This hazard rate then dropped to very low levels for all three groups after one year of age.

Table 5-7. Post-operative hazard rates (instantaneous monthly risks of death) prior to definitive surgery for the 183 patients with tricuspid atresia who underwent one of the three main palliative procedures

Months	Systemic-to-pulmonary arterial shunt	Banding of the pulmonary trunk	Banding of PT and aortic arch repair
0 - 1	0.102	0.138	0.429
1 - 3	0.017	0.000	0.294
3 - 6	0.012	0.000	0.000
6 - 12	0.017	0.000	0.067
12 - 24	0.009	0.010	0.000
24 - 60	0.003	0.000	0.011
60 - 120	0.002	0.000	0.000

PT, pulmonary trunk

Five other patients underwent an initial unidirectional cavopulmonary connection (Glenn procedure) with one operative and one unexpected late death at age 2.5 years. The remaining three patients were alive after Fontan-type procedures at ages 12.5, 13 and 13 years. Finally, six patients underwent various other miscellaneous initial palliative procedures with three operative deaths, as detailed in Table 5-6.

5.6 Outcome of the patients who did not undergo palliative surgery

Only 43 out of the 237 patients (18%) with tricuspid atresia did not undergo palliative surgery. Six neonates initially presented with severe low cardiac output and acidosis to the tertiary centres and were considered unfit to withstand palliative surgery (at that time). They all died soon after being first assessed.

A further 16 infants had such complex or severe lesions that palliative surgery was not felt at the time of their initial assessment at the tertiary centres, to offer any long term chance of definitive repair. The decision not to offer surgery was made on an arbitrary and individual basis in consultation with the infants' parents. In fact, at retrospective review, all were deemed to be unsuitable when first seen for future definitive surgery. Table 5-8 compares the outcome of these patients with a similar cohort of patients who were palliated. The fate of both groups was equally dismal with only four out of the 33 patients surviving to the end of the follow-up period. Further details of their outcome are given in Section 5.7.3 (page 154).

Table 5-8. Morphology and outcome of the 33 patients with tricuspid atresia deemed retrospectively to be unsuitable for a future Fontan-type procedure at initial presentation

	No surgical palliation	Palliated
Coarctation of the aorta and subaortic obstruction	3	6
Isolated subaortic stenosis	6 (2)	3 (1)
Severe pulmonary arterial distortions	1	3 (1)
Severe left AV valve regurgitation	1	0
Double outlet rudimentary ventricle, subaortic stenosis & severe pulmonary stenosis (underwent construction of systemic-to-pulmonary arterial shunts)	0	2
Complex anomalies †		
Right atrial isomerism, common AV valve with imperforate right valve, obstructed TAPVC	1	0
Dominant right or indeterminate ventricle with either pulmonary atresia or severe pulmonary stenosis	3	2
Straddling left AV valve, coarctation of the aorta, complete heart block	1	0
Common arterial trunk, coarctation	1	0
	17 (2)	16 (2)
Total:	**33 out of 237 patients (14%)**	

The numbers in parentheses indicate the patients who survived the follow-up period.

† All these patients are theoretically suitable but were considered at the time to have such complex anatomy that they would never become candidates for a Fontan-type operation.

AV, atrioventricular; TAPVC, totally anomalous pulmonary venous connections.

Finally, 21 patients did not require palliative intervention during follow-up, due to the presence of relatively balanced physiology throughout the study period.

5.7 Suitability for definitive surgery

5.7.1 Suitability for a Fontan-type operation at initial presentation

All but 33 patients (14%) with tricuspid atresia were considered by retrospective review to be potential candidates for a future Fontan-type procedure when first seen at the tertiary centres (Table 5-8). The most common individual adverse feature found was subaortic stenosis (18 patients), whilst eight patients were deemed to be unsuitable for future definitive surgery (at that time) due to the complexity of their lesions (Table 5-8).

Actuarial survival was predictably better for the remaining 204 potentially suitable patients than for these 33 patients: 78% versus 36% at age one year, 58% versus 21% at age five years and 46% versus 14% at age ten years, respectively ($p < 0.001$, log rank test; Figure 5.7).

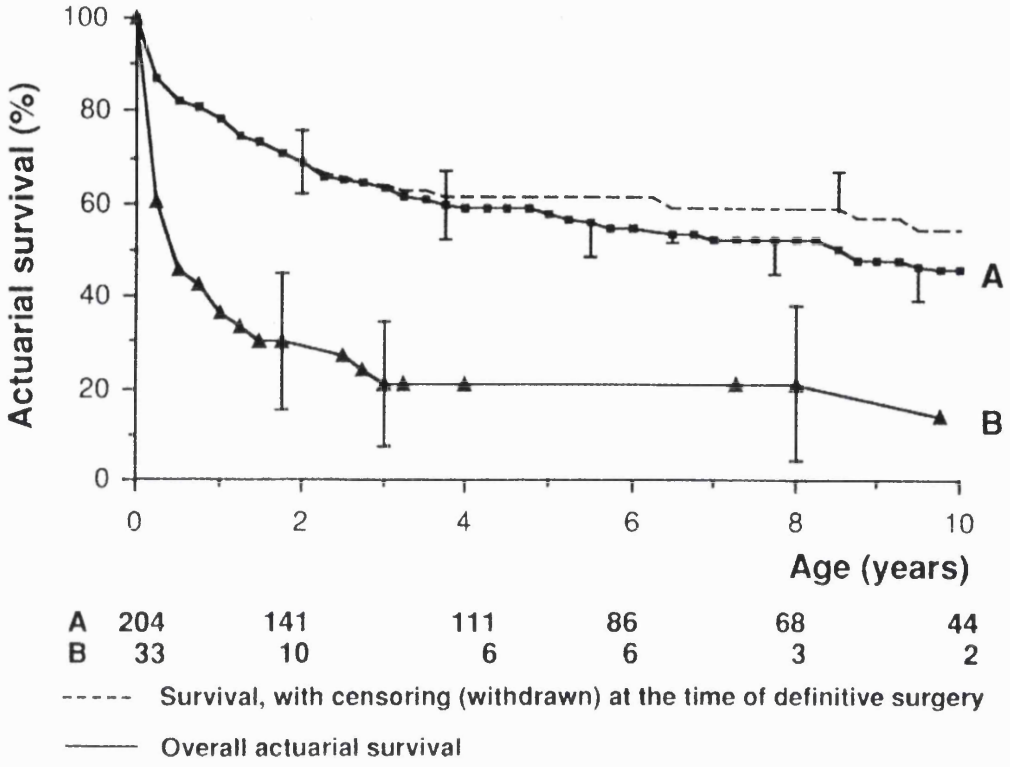

Figure 5.7. Actuarial survival curves of the 204 patients with tricuspid atresia considered retrospectively to be potentially suitable for a future Fontan-type procedure at initial presentation (**Curve A**) and the 33 patients considered unsuitable for such surgery (**Curve B**). The latter fared worst ($p < 0.001$). The upper interrupted curve refers to survival before definitive surgery (see Chapter 3, page 73). The vertical bars are the actuarial 95% confidence limits, and the numbers are the remaining patients still being followed at that time, with reference to the time scale of the x-axis. Refer to the text for the percentage survival details.

5.7.2 Outcome of the patients considered retrospectively to be suitable for a Fontan-type operation at initial presentation

By actuarial calculations, only 72% of these 204 patients remained alive and still suitable for a future Fontan-type procedure at 1.5 years of age and only 59% at four years of age (Figure 5.8).

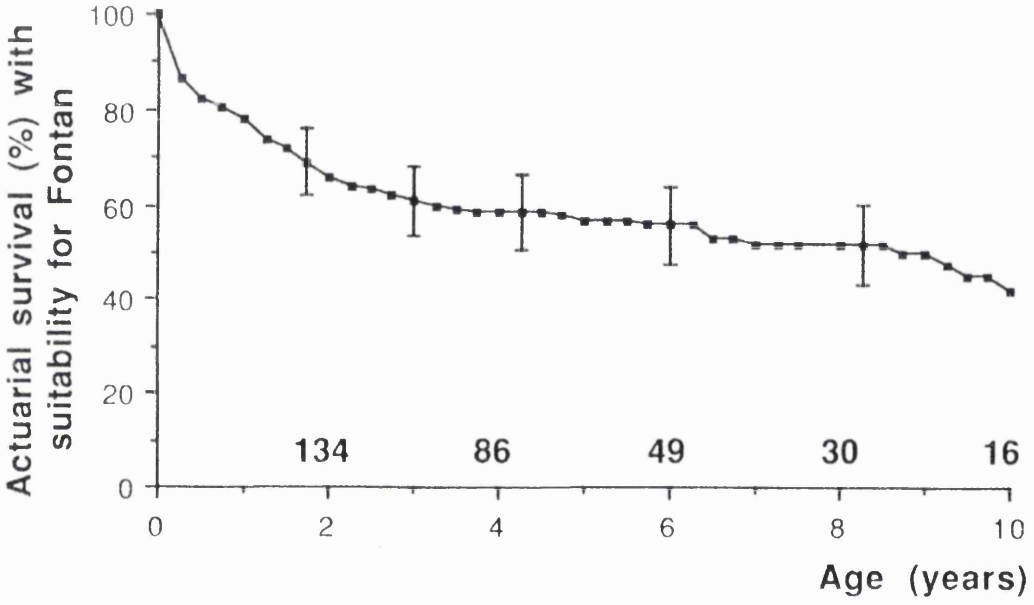

Figure 5.8. Actuarial survival curve free of adverse events (death or new adverse feature which would preclude a future Fontan-type operation) of the 204 patients with tricuspid atresia considered retrospectively to be potentially suitable for such future surgery at initial presentation. The patients were withdrawn alive at the time of definitive surgery (see Chapter 3, page 73). The vertical bars are the actuarial 95% confidence limits, and the numbers are the remaining patients still being followed at that time, with reference to the time scale of the x-axis. Refer to the text for further details.

Death occurred most frequently following palliative surgery (23 patients, 11%). As many as 18 patients (9%) suffered late unexpected deaths, 17 before age four years (Figure 5.9, Table 5-9). New adverse features became evident in 32 patients (16%), most often in the first four years of life (Figure 5.9, Table 5-9). The most frequent of these was subaortic stenosis, which developed in nine patients: eight after banding of the pulmonary trunk either in isolation (two patients) or together with relief of aortic coarctation (six patients); and in one patient who had received no palliative surgery (due to the presence of pulmonary infundibular stenosis). Further details are given in Chapter 6 (page 156).

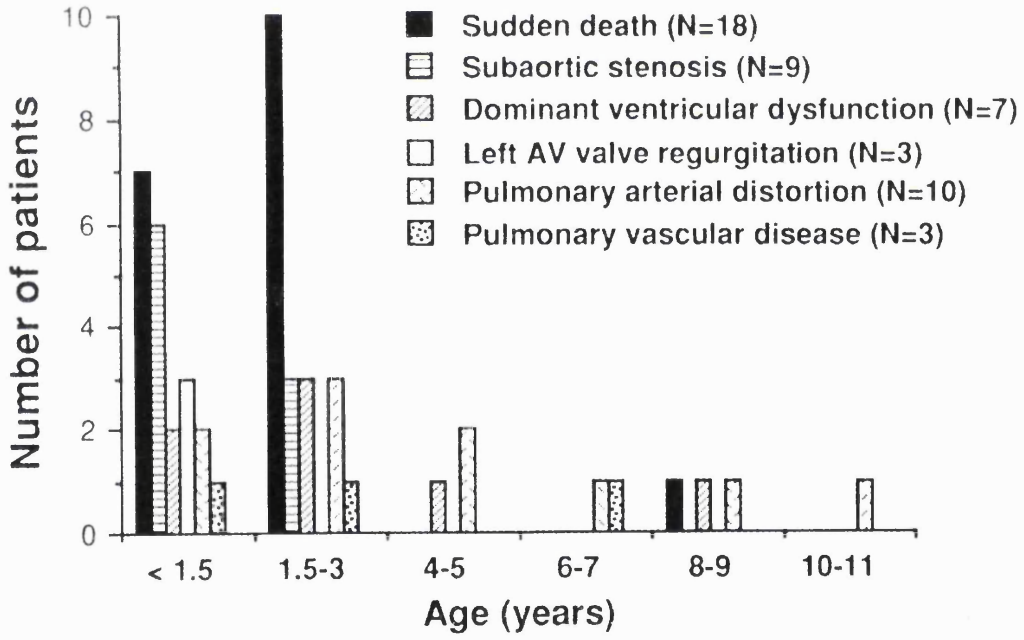

Figure 5.9. Bar chart showing the age at which sudden death occurred, or when an adverse feature which precluded a future Fontan-type procedure first became evident, during the follow-up of the 204 patients with tricuspid atresia considered retrospectively to be potential candidates for such future surgery at initial presentation.
AV, atrioventricular.

Table 5-9. Detailed fate of the 204 patients with tricuspid atresia considered to be potentially suitable for a Fontan-type procedure at initial presentation

	No surgical palliation N = 28 *	Systemic-to-pulmonary arterial shunt N = 128	Isolated banding of the pulmonary trunk N = 28	Banding of pulmonary trunk & aortic arch repair N = 11	Other operation N = 9	Total N = 204
Death prior to definitive surgery without new adverse features:						
Presentation with low cardiac output	6					6
Sudden late death	3	14	0	0	1	18
At palliative surgery		14	3	4	2	23
Blocked SPA shunt		3				3
Miscellaneous †	2	8				10
New adverse features precluding a Fontan-type procedure:						
Subaortic stenosis	1	0	2	6	0	9
Dominant ventricular dysfunction	0	6	1	0	0	7
Pulmonary arterial distortion	0	5	0	0	0	5
Pulmonary arterial distortion & PVD	0	4	0	0	1	5
Pulmonary vascular disease - isolated	1	0	1	0	1	3
Left atrioventricular valve regurgitation	0	3	0	0	0	3
Pulmonary arterial distortion not precluding a Fontan-type procedure ‡	0	13 ‡	1 ‡	0	1 ‡	15 ‡
Lost to follow-up	1	4	2	0	0	7
Suitable for a Fontan-type procedure at repeat catheterisation:						
Awaiting repair at end of follow-up period	3	5	3	0	0	11
Fontan procedure (operative death):						
- atrio-pulmonary connection	4	47(7)	10(4)	0	1	62
- atrio-ventricular connection	6	7(3)	4(2)	0	2	19
Total cavopulmonary connection (operative death)	1	8(2)	2	1 #	1	13

* Seven out of these 28 patients died prior to intended surgical intervention (six due to their initial presentation with acidosis and low cardiac output & one at operative separation of conjoined twins). The remaining 21 patients had balanced physiology and electively received no palliation.

† There were ten deaths: three patients at catheterisation (one not palliated, two at over 1.5 years of age); four patients due to pneumonia; one patient due to meningitis; one patient due to a pulmonary embolus at 3.5 years of age; and one patient at operative separation of conjoined twins (not palliated).

‡ These numbers are not included in the overall total.

This patient is the only one in this subgroup with double outlet from the dominant ventricle ventriculo-arterial connections and so not at risk of developing subaortic stenosis.

PVD, pulmonary vascular disease; SPA, systemic-to-pulmonary arterial.

Multiple systemic-to-pulmonary arterial shunts were constructed for 39 patients. This subgroup accounted for one third of those who acquired adverse risk factors to a successful future Fontan-type procedure: nine out of the ten patients who developed severe pulmonary arterial distortion(s), three out of the six patients who developed marked dominant ventricular dysfunction and one out of the three patients whose left atrioventricular valve became severely regurgitant. In addition, ten out of the 15 patients who developed pulmonary arterial distortion sufficient to require surgical attention, but not preclude a Fontan-type operation, had undergone multiple shunt procedures. This was a significantly higher proportion when compared to the 96 patients who had only had a single shunt constructed (Table 5-9, $p < 0.001$).

5.7.2.1 Outcome with respect to management

Survival as suitable candidates for a Fontan-type operation at the end of follow-up period was similar for the patients with balanced physiology (who had required no surgical palliation), for those patients who had required construction of a systemic-to-pulmonary arterial shunt and for those patients who had undergone isolated banding of the pulmonary trunk: 14 out of 20 patients (70%), 68 out of 124 patients (55%) and 19 out of 26 patients (73%) alive and suitable, respectively (Table 5-9). In contrast, only one out of the 11 patients who underwent banding of the pulmonary trunk together with aortic arch surgery remained alive and suitable over the follow-up period ($p < 0.01$, Table 5-9). These calculations excluded the seven patients lost to follow-up in infancy.

The multivariate analysis was then repeated using data only from the 204 potentially suitable patients. This was more representative of patients with tricuspid atresia, who would usually be expected to be potentially suitable for future definitive surgery at initial presentation. The dual end-points of death and becoming unsuitable for a Fontan-type procedure were consequently used. This resulted in a refinement of the additive index (Table 5-4) and a new cross-tabulation of outcome (Table 5-10), with increased specificity to the more common sub-groups of patients with tricuspid atresia.

5.7.3 Outcome of the patients considered retrospectively to be unsuitable for definitive repair at initial presentation

Actuarial survival was very poor in this group (Figure 5.7, curve B). In 17 of these 33 patients, an arbitrary decision was taken not to embark on surgery, as their anatomy was considered to be so 'complex' that the clinicians at the time of initial assessment felt that surgical intervention offered no longer term chance of a successful Fontan-type operation. Although the other 16 patients were palliated, their outcome was equally poor (Table 5-8), as was the case for similar cohorts of patients with double inlet ventricle. None of this group ever became suitable candidates for Fontan-type surgery during the follow-up period.

Table 5-10. Actual patient outcome versus multivariate derived additive index scores for the 204 patients with tricuspid atresia deemed suitable at initial presentation, with death or unsuitability for a Fontan operation treated as adverse events

	Adverse event prior to palliation			Adverse event after palliation			No adverse event prior to operation			No adverse event after palliation			Definitive † surgery		
Total additive risk score	N	%	median survival (years)	N	%	median survival (years)	N	%	median follow-up (years)	N	%	median follow-up (years)	N	%	median follow-up (years)
≤ 3 (N = 8)													8	100	4.3
- 2 (N = 20)				1	5	8.5	2	10	16.8	4	20	5.3	13	65	5.5
- 1 (N = 59)	2	3	0.9	16	27	1.4	2	3	6.4	5	9	5.6	34	58	4.4
0 (N = 71)	3	4	1.0	27	38	0.8				11	16	9.3	30	42	4.6
+ 1 (N = 25)				13	52	1.1				6	24	8.2	6	24	5.2
+ 2 (N = 5)	1	20	0.2	1	20	0.1				1	20	10.3	2	40	2.5
≥ 3 (N = 16)	5	31	3 days	10	63	0.4				1	6	4.2			
Total (% 204)	11	(5)		68	(33)		4	(2)		28	(14)		93	(46)	

† Signifies definitive surgery by means of a Fontan-type operation, exclusive of operative mortality.

This table allows assessment of the fate of new patients at initial presentation, by examining the outcome of previous patients who had the same total score as the new patient, as derived from the additive index shown in Table 5-4, column 2. See the legend below Table 5-5 for details of how to use this table and for an example. The same reservations expressed there also apply.

Chapter 6

Results of the 102 patients with the substrate for subaortic stenosis

6.1 Morphological characteristics

All of the 102 patients had a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow. The type of atrioventricular connection was double inlet in 56 patients (55%) and absent right (tricuspid atresia) in the remaining 46 patients (45%). All but one patient had the usual atrial arrangement (Table 6-1). Systemic outflow obstruction was found at initial presentation in 63 infants (62%) at either subaortic level (11 patients), the level of the great arteries (35 patients) or both (17 patients). Additional anatomical details are shown in Tables 6-1 and 6-2.

Table 6-1. Morphological features at initial presentation of the 102 patients with the substrate for subaortic stenosis †

Feature	Number
Atrial arrangement	
Usual (solitus)	101 (99%)
Right atrial isomerism ‡	1 (1%)
Type and mode of atrioventricular connection	
Absent right (tricuspid atresia) with left atrioventricular valve connected to the dominant left ventricle	46 (45%)
Double inlet left ventricle	56 (55%)
- via two atrioventricular valves	49 (48%)
- via a common atrioventricular valve	7 (7%)
Aortic arch lesion	
Absent	50 (49%)
Coarctation of aorta	45 (44%)
Interrupted aortic arch	7 (7%)
Subaortic lesion	
Absent	74 (72%)
Restrictive ventricular septal defect ± narrow right ventricular infundibulum	28 (28%)

† All of the patients had a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow.

‡ This patient also had obstructed totally anomalous pulmonary venous connections.

Table 6-2. Type of systemic outflow obstruction at initial presentation with respect to the type of atrioventricular connection of the 102 patients with the substrate for subaortic stenosis †

	Double inlet ventricle	Tricuspid atresia	Total
Isolated subaortic stenosis	2	9	11 (11%)
Isolated aortic arch obstruction	21	14	35 (34%)
Both subaortic stenosis & aortic arch obstruction	8	9	17 (17%)
Neither subaortic stenosis nor aortic arch obstruction	25	14	39 (38%)
Totals	**56**	**46**	**102**

† All of the patients had a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow.

The patients were retrospectively divided into three morphological groups based on their anatomy as documented at initial presentation to the tertiary centres (Figure 6.1): those with subaortic stenosis (28 patients), those without subaortic stenosis but with aortic arch obstruction (35 patients) and those without either subaortic stenosis or aortic arch obstruction (39 patients).

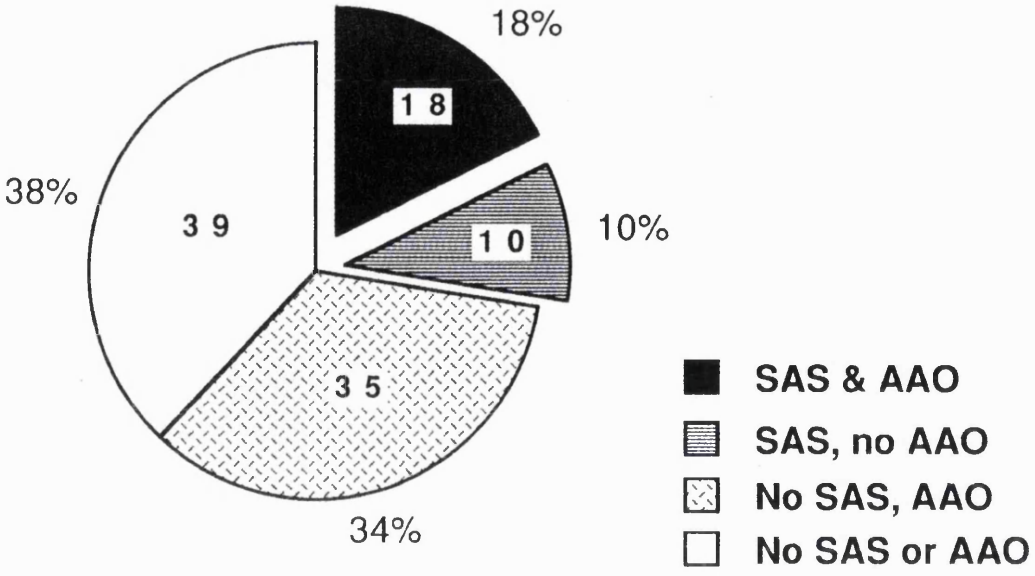

Figure 6.1. Incidence of systemic outflow obstruction at initial presentation in the 102 infants with double inlet ventricle or tricuspid atresia and with the morphological substrate for having or developing subaortic stenosis (see text).
AAO, aortic arch obstruction; SAS, subaortic stenosis.

6.2 Outcome of the three patient groups

6.2.1 Patients with subaortic stenosis at initial presentation

In these 28 patients subaortic stenosis was already apparent when first assessed at the tertiary centres (Tables 6-1 and 6-2). Surgery was not performed in 13 (46%) of these infants as their anatomy was considered at the time to be too complex to offer any long term chance of successful definitive surgery (Figure 6.2). This decision was made on an arbitrary and individual basis in conjunction with the infants' parents. Only two of these patients survived infancy, to ages six and eight years, and both inevitably developed pulmonary vascular disease.

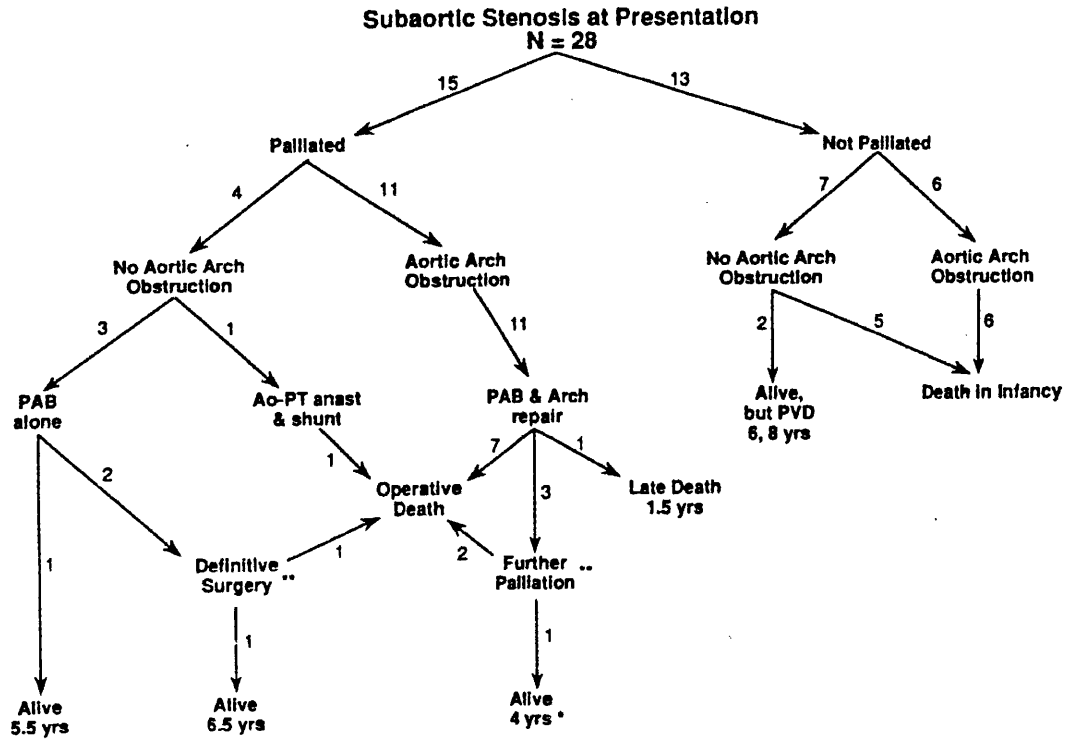

Figure 6.2. Outcome of the 28 infants with double inlet ventricle or tricuspid atresia and with subaortic stenosis at initial presentation.

* Patient fulfilled criteria for a Fontan-type procedure when recatheterised.

** See Table 6-3 for details of these operations undertaken to relieve subaortic stenosis.

Ao-PT anast and shunt, aorto-pulmonary trunk anastomosis and systemic-to-pulmonary arterial shunt; PAB, pulmonary artery banding; PVD, pulmonary vascular disease.

Palliative surgery was performed on the other 15 infants, as detailed in Figure 6.2. All but one patient underwent banding of the pulmonary trunk together with relief of aortic arch obstruction (where necessary), without dealing with the subaortic narrowing. There were eight early deaths (53%) and one late death from pneumonia at age 1.5 years. Three of those surviving went on to have further palliative surgery to deal with the subaortic stenosis, with one survivor (Table 6-3). This latter patient was found to fulfil criteria for a Fontan-type procedure when recatheterised at four years of age. In two

patients the subaortic lesion was dealt with at the time of definitive surgery, with one death (Table 6-3). One patient, aged 5.5 years at the end of the follow-up period, awaits similar surgery. Thus, only five out of these 28 patients (18%) survived follow-up, and only one of these underwent a successful definitive operation.

6.2.2 Patients without subaortic stenosis but with aortic arch obstruction at initial presentation

Of these 35 patients, 13 received no surgical palliation. Nine neonates were considered to be too sick with low cardiac output and acidosis at initial presentation to the tertiary centres to withstand such surgery (all with a pH of less than 7.20 for over six hours). The remaining four patients had anatomy that was considered (at the time) to be too complex to offer any longer term chance of successful definitive repair. Again, this decision was made on an arbitrary and individual basis in conjunction with the infants' parents. The one patient who survived past infancy died suddenly at age 3.5 years (Figure 6.3).

The remaining 22 patients (twenty with coarctation of the aorta, two with an interrupted aortic arch) all underwent banding of the pulmonary trunk together with aortic arch repair at a median age of four weeks (Figure 6.3). There were ten operative deaths (45%). Subaortic stenosis was diagnosed in ten out of the 12 survivors (83%) by two years of age. Four out of these ten patients died soon thereafter. One of the remaining two patients had been lost to follow-up but died suddenly at three years of

age and did not undergo a post-mortem examination. The final patient died at two years of age with established pulmonary vascular disease (Figure 6.3).

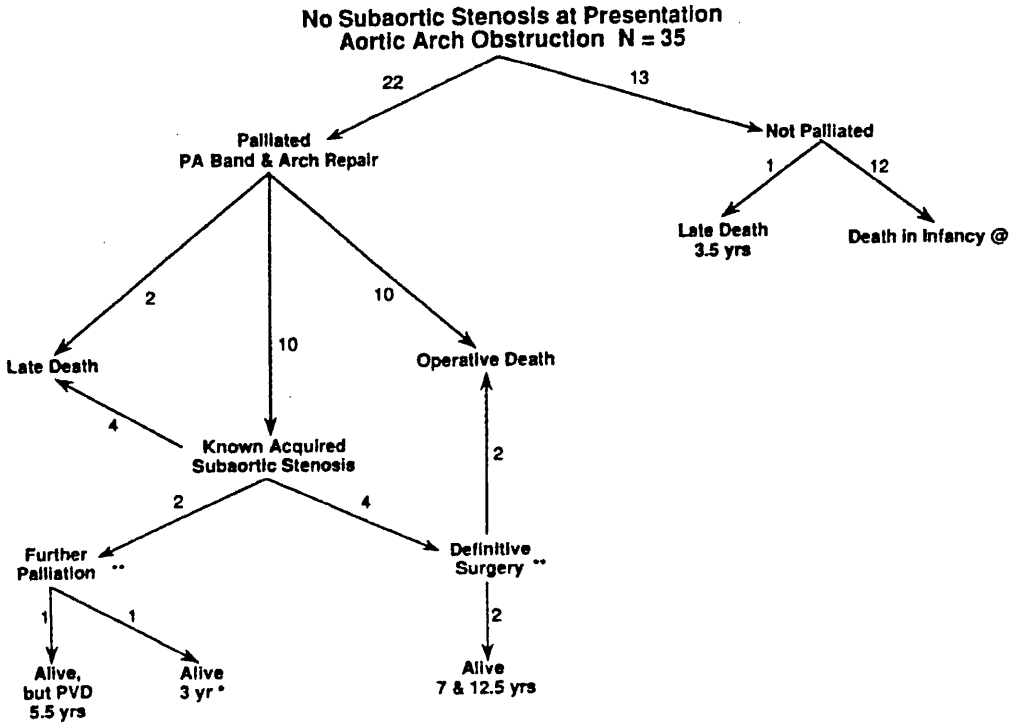

Figure 6.3. Outcome of the 35 infants with double inlet ventricle or tricuspid atresia without subaortic stenosis but with aortic arch obstruction at initial presentation.

@ This group includes one patient with right atrial isomerism and obstructed totally anomalous pulmonary venous connections.

* Patient fulfilled criteria for a Fontan-type procedure when recatheterised.

** See Table 6-3 for details of these operations undertaken to relieve subaortic stenosis.

PA Band, pulmonary artery banding; PVD, pulmonary vascular disease.

Table 6-3. Operative procedures, where undertaken, to relieve subaortic stenosis after initial palliative surgery (16 out of 43 patients)

	Initial palliative procedure in patients with subaortic stenosis at presentation (14 out of 28 patients)				Initial palliative procedure in patients who later acquired subaortic stenosis (11 out of 15 patients)			
	Banding of pulmonary trunk & repair of aortic arch lesion N = 3 out of 11		Isolated banding of the pulmonary trunk N = 2 out of 3		Banding of pulmonary trunk & repair of aortic arch lesion N = 6 out of 10		Isolated banding of the pulmonary trunk N = 5 out of 5	
	age (yr)	alive/dead	age (yr)	alive/dead	age (yr)	alive/dead	age (yr)	alive/dead
Relief of subaortic stenosis as further staged palliative surgery								
Aorto-pulmonary trunk anastomosis & SPA shunt (N = 3) ‡	0.3	dead			2.0	alive †	4.0	dead
Enlargement of VSD ± RV outflow tract (N = 4)	0.3	alive †			4.0	alive *	3.5	alive
	1.5	dead						
Left ventricle-descending aorta conduit (N = 1)							1.5	dead
Relief of subaortic stenosis combined with definitive Surgery								
Aorto-pulmonary trunk anastomosis & modified Fontan (N = 7)			1.5	dead	1.0	dead	2.0	dead
			6.0	alive	4.5	dead	2.3	dead
					11.0	alive		
Enlargement of VSD & modified Fontan (N = 1)					2.5	alive		

‡ One additional patient had an aorto-pulmonary anastomosis and systemic-to-pulmonary arterial shunt as *initial* palliation at age one year (operative death).

† These patients fulfilled the criteria for a Fontan-type operation when recatheterised. * This patient had established pulmonary vascular disease at the time of surgery.

RV, right ventricular; SPA, systemic-to-pulmonary arterial; VSD, ventricular septal defect; yr, years.

The surviving six patients subsequently underwent further surgery to relieve their acquired subaortic stenosis (Table 6-3). In four patients, this was performed at the time of definitive surgery, with two survivors. Both patients who underwent a further palliative procedure without attempted definitive repair survived, although when recatheterised at age three years, only one patient fulfilled criteria for a future Fontan-type procedure, the other having developed pulmonary vascular disease.

Thus, actuarial survival free of subaortic stenosis was dismal for this group (Figure 6.4). All of the survivors of initial palliation went on to develop subaortic stenosis by three years of age. Only four out of the 22 patients (18%) who had undergone an aortic arch procedure together with banding of the pulmonary trunk, survived the follow-up period. Only one of these patients achieved suitability for a Fontan-type procedure.

6.2.3 Patients without either subaortic stenosis or aortic arch obstruction at initial presentation

Palliative surgery was not undertaken in six of these 39 patients. One patient died at initial catheterisation, whilst two patients did not undergo surgery due to the presence of severe atrioventricular valve regurgitation and both died in infancy. A further patient was found to already have evidence of pulmonary vascular disease at first assessment, but survived the follow-up period at age 3.5 years. The remaining two patients who did not receive surgical palliation were first seen in the early study period and were not offered surgery. Both survived follow-up to age 11 years, but with established pulmonary vascular disease (Figure 6.5).

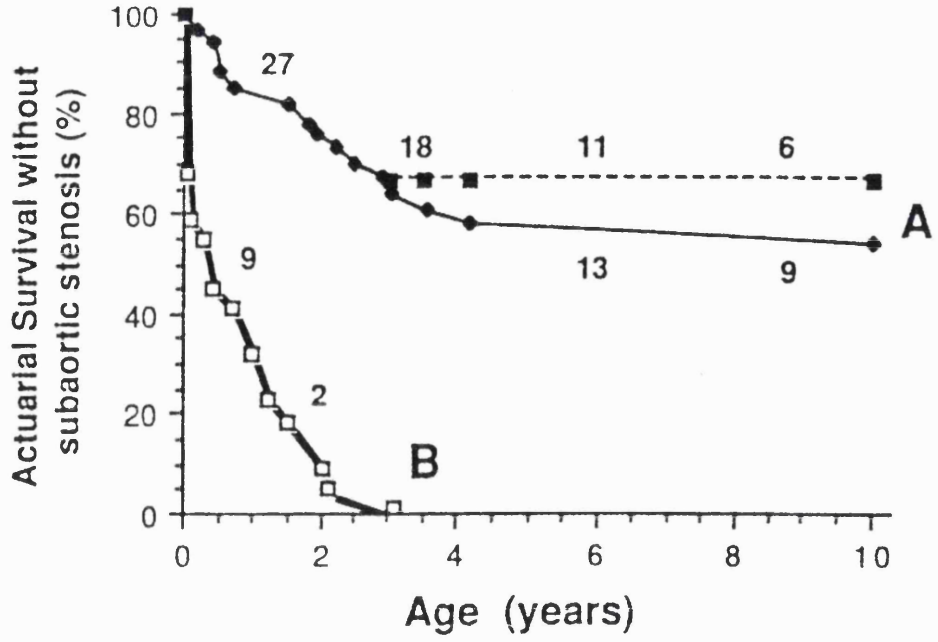

Figure 6.4. Kaplan-Meier actuarial survival curves free of subaortic stenosis, comparing the 33 patients with double inlet ventricle or tricuspid atresia who underwent isolated banding of the pulmonary trunk (**Curve A**) with the 22 patients who underwent banding of the pulmonary trunk together with aortic arch repair (**Curve B**). The latter patients fared worst ($p < 0.0001$). The interrupted line indicates survival if the patients were additionally withdrawn as alive at the time of definitive surgery (see Chapter 3, page 73). The numbers are the remaining patients still being followed at that time, with reference to the time scale of the x-axis.

The remaining 33 patients underwent banding of the pulmonary trunk at a median age of 22 weeks. The operative mortality was 12%, which was far less than that for patients who required additional aortic arch repair: four out of 33 patients (12%) compared to ten out of 22 patients (45%), respectively ($p < 0.01$). Two patients died suddenly at ages three months and three years, and one overseas patient was lost to follow-up.

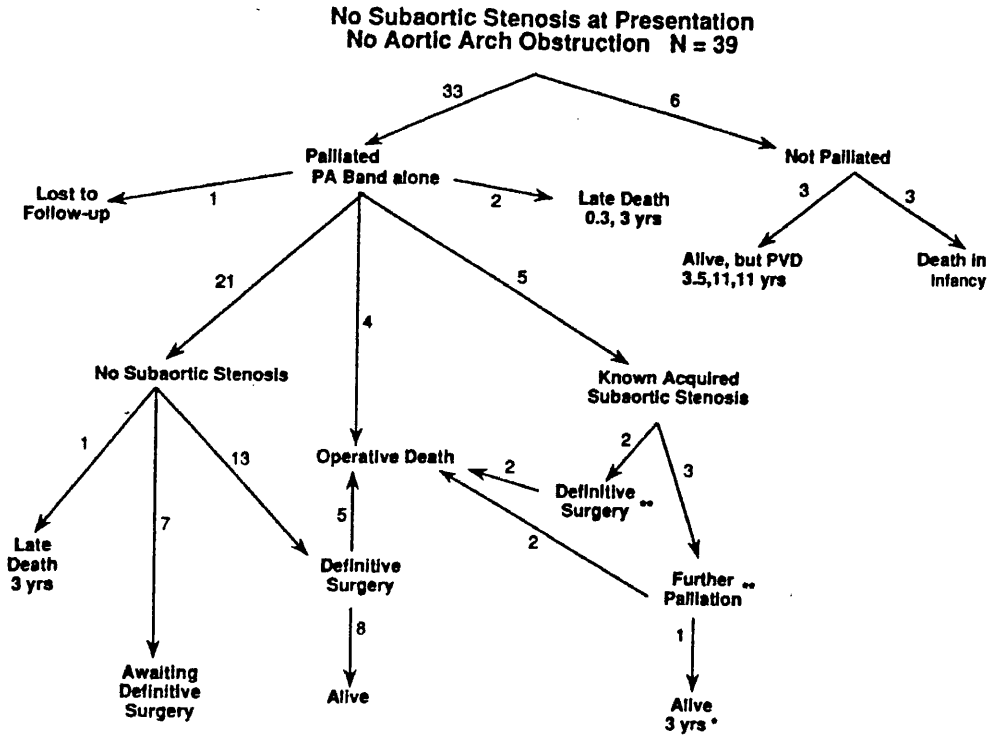

Figure 6.5. Outcome of the 39 patients with double inlet ventricle or tricuspid atresia, but without either subaortic stenosis or aortic arch obstruction at initial presentation.

* Patient fulfilled criteria for a Fontan-type procedure when recatheterised.

** See Table 6-3 for details of these operations undertaken to relieve subaortic stenosis.

PA Band, pulmonary artery banding; PVD, pulmonary vascular disease.

Subaortic stenosis developed in five out of the remaining 26 patients (22%). This was recognised in all patients by 2.5 years of age, with a mean follow-up period of 8.5 years for the entire group. The actuarial survival rate free of subaortic stenosis was significantly better than for those palliated with additional relief of aortic arch obstruction (Figure 6.4, $p < 0.0001$). All five patients with new subaortic stenosis underwent further surgery to relieve this (Table 6-3). In two children the diagnosis of subaortic stenosis was not made until the time of definitive surgery. Both failed to survive the procedure. The other three patients underwent an additional palliative

procedure to relieve the subaortic narrowing, with only one survivor. This latter patient was found to be suitable for a future Fontan-type procedure when recatheterised.

Recatheterisation was performed in 19 out of the 21 patients who did not develop subaortic stenosis. All but one patient fulfilled established criteria for a future Fontan-type procedure. The one patient found to be unsuitable had marked left ventricular dysfunction which first became evident at age 1.5 years and from which he died soon thereafter.

6.3 Identification of patients at high risk of developing subaortic stenosis

The ratio of ventricular septal defect diameter to ascending aorta diameter at the time of initial presentation to the tertiary centres was successfully assessed retrospectively in 37 out of the 39 patients without subaortic stenosis when first seen (Figure 6.6). All had survived over 0.4 years after their first palliative procedure (banding of the pulmonary trunk with or without additional aortic arch surgery) and none were lost to follow-up. Of relevance is that this ratio could not be calculated in one out of the five patients in this group who later developed subaortic stenosis after isolated banding of the pulmonary trunk. This was because the 1975 biplanar cineangiogram did not adequately profile the ventricular septal defect. Nevertheless, the ratio of 0.60 ± 0.08 obtained for the remaining four of these five patients, was significantly less than that of 1.03 ± 0.15 found for the 22 patients who did not develop subaortic stenosis during follow-up after the same procedure (Figure 6.6; $p < 0.001$), as illustrated in Figures 6.7 and 6.8.

Interestingly, the ratios measured in the 12 patients who required additional aortic arch surgery and who all went on to develop subaortic stenosis, were not found to lie below this cut off level. Their ratio was 0.82 ± 0.15, with a range of 0.3 to 1.0 (Figure 6.6).

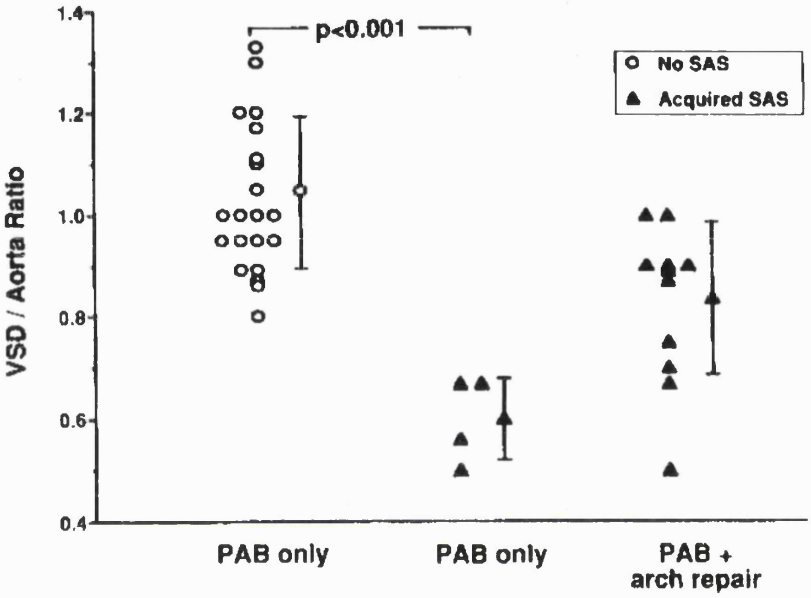

Figure 6.6. Ratios at initial presentation of ventricular septal defect size to ascending aorta diameter for the 39 infants without subaortic stenosis at initial presentation, and who received and survived an initial palliative procedure. The data was incomplete for two patients (see text). There was a significant difference in the ratios between the patients who did, and those who did not, develop subaortic stenosis after isolated banding of the pulmonary trunk.

PAB, pulmonary artery banding; SAS, subaortic stenosis; VSD, ventricular septal defect.

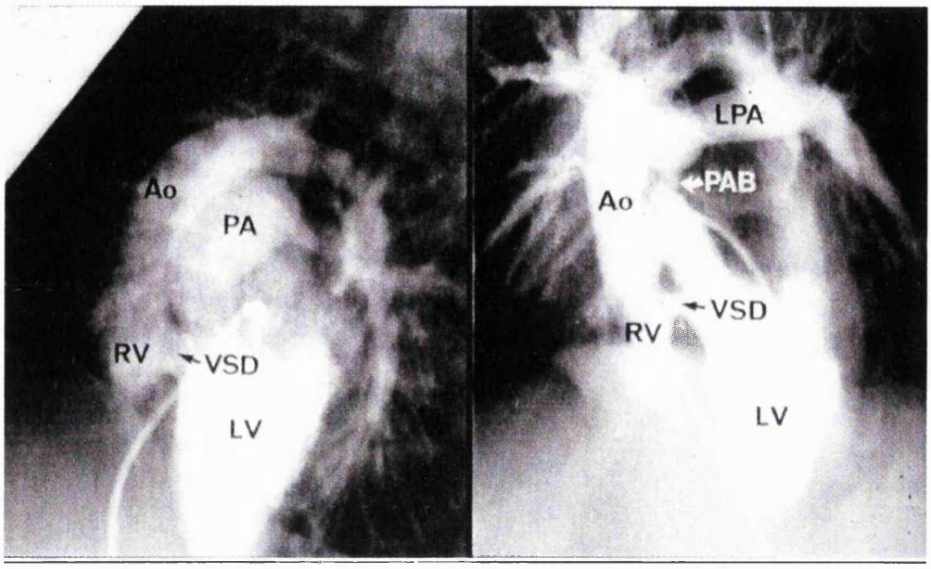

Figure 6.7. Angiographic frames from a patient with tricuspid atresia, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow with a normal aortic arch, at age four days (left panel) and at age 1.9 years (right panel), when subaortic stenosis first became evident. This neonate underwent isolated banding of the pulmonary trunk at age two weeks. The ventricular septal defect to ascending aorta ratio was 0.7 at initial presentation (left panel).

Ao, aorta; LPA, left pulmonary artery; LV, left ventricle; PA, pulmonary artery; PAB, pulmonary artery band; RV, right ventricle; VSD, ventricular septal defect.

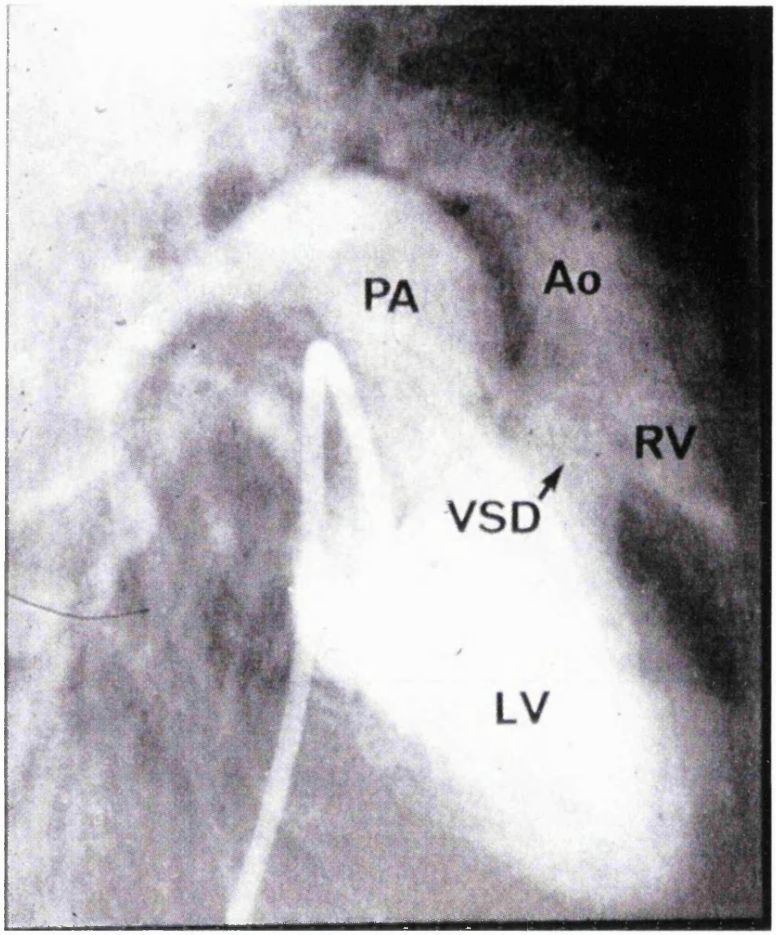

Figure 6.8. Angiographic frame from an infant with tricuspid atresia, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow with a normal aortic arch, at age seven weeks. This patient did not develop subaortic stenosis after isolated banding of the pulmonary trunk at age two months. The ventricular septal defect to ascending aorta ratio was 1.2 at initial presentation.

Ao, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; VSD, ventricular septal defect.

The ratio between the ascending aorta and pulmonary trunk diameters was successfully measured retrospectively in 37 out of these same 39 patients (Figure 6.9).

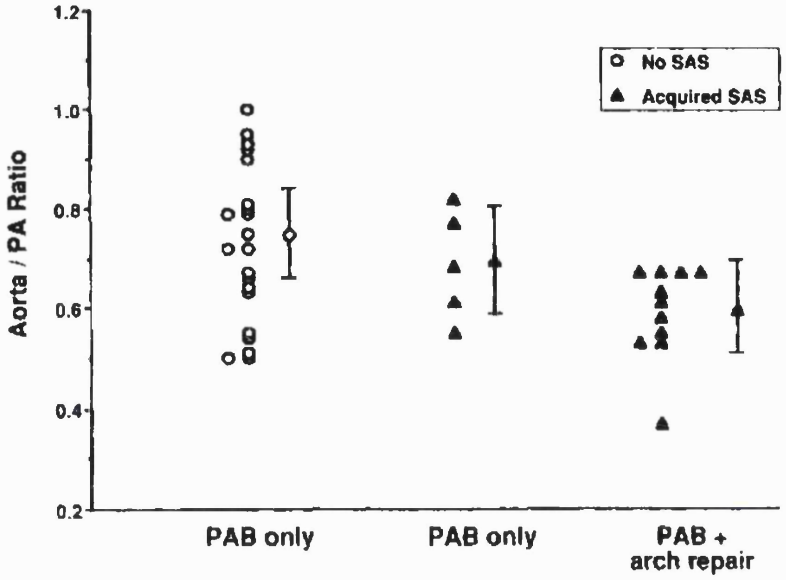

Figure 6.9. Ratios at initial presentation of the ascending aorta to pulmonary artery diameters for the 39 infants without subaortic stenosis when first seen, and who received and survived an initial palliative procedure. The data were incomplete for two patients (see text). There was no significant difference in the ratios between any of the patient groups.
PA, pulmonary artery; PAB, pulmonary artery banding; SAS, subaortic stenosis.

This ratio was not found to discriminate between any of these groups of patients: 0.71 ± 0.15 in those who underwent isolated banding of the pulmonary trunk, without later acquiring subaortic stenosis; 0.69 ± 0.11 in the five patients who did develop subaortic stenosis after isolated banding of the pulmonary trunk; and 0.59 ± 0.09 in the 12 patients who underwent banding of the pulmonary trunk together with relief of aortic arch obstruction.

Chapter 7

General discussion and critical review of methodology

Currently, at most centres the accepted aim of management in infancy and of initial palliative surgery for patients with double inlet ventricle and tricuspid atresia, is to both ensure survival and to establish and maintain suitable haemodynamics and anatomy for an eventual Fontan-type procedure or ventricular septation operation (for those with double inlet ventricle), at an older age (Anderson et al, 1987b, 1987c; Kirklin and Barratt-Boyes 1993a, 1993b). This is despite the fact that recent reports have questioned the longer term well-being of patients who underwent definitive repair in the early Fontan era (Fontan et al, 1990; Driscoll et al, 1992), as discussed in Chapter 10 (page 191). The influences on survival and subsequent suitability for definitive repair of different medical and surgical management strategies undertaken by the tertiary centre once such patients present in infancy, are crucial to these goals, but to date they have not been studied in an unselected population in the Fontan era.

This innovative study examines the fate of 428 consecutive patients with double inlet ventricle and tricuspid atresia from the time of their initial presentation in infancy to a tertiary centre. It represents the largest series of such patients reported to date and the findings differ fundamentally from previous, less comprehensive reports, due to the morphological spectrum and variety of risk factors encountered. In this series adverse features were relatively common, whilst favourable ones were comparatively few. For

the first time, virtually all the anatomic variants known to occur in these patients are detailed and considered in context with respect to the lesions as a whole. The study goes on to analyse the outcome of the two overall groups and their various subgroups in terms of mortality and suitability for definitive surgery, as well as examining the needs, benefits and adverse effects of palliative surgery on these two outcome measures. Importantly, the data and methodology facilitate the prediction of the potential fate of a new patient with any morphological variant of either lesion in respect to both survival and the prospect of undergoing a low risk definitive operation, based on the outcome of the patients in this study. In summary, a structured and comprehensive framework has been provided to assist rational therapeutic decision-making for individual infants with any form of tricuspid atresia or double inlet ventricle.

7.1 Critical review of methodology

7.1.1 Patient selection

This retrospective study exclusively examines patients with tricuspid atresia and double inlet ventricle and excludes those with mitral atresia, despite the fact that a study of the three groups together would cover all those with an underlying univentricular atrioventricular connection. This restriction was imposed due to the common difficulty in differentiating patients with true mitral atresia, who usually have a diminutive left ventricle, from those patients labelled as having the 'hypoplastic left heart syndrome', using historical data. This distinction is important, as the latter group are characterised as having aortic atresia and usually biventricular atrioventricular connections, albeit with a severely hypoplastic mitral valve. Aortic atresia is uncommon with true mitral

atresia and is rarely encountered in hearts with tricuspid atresia or double inlet ventricle. Initial surgery for patients with aortic atresia is clearly distinct from that used for most patients with tricuspid atresia or double inlet ventricle, and in most centres carries a far higher mortality (Kirklin and Barratt-Boyes, 1993c). Furthermore, these risks have meant that until relatively recently many patients labelled as having the hypoplastic left heart syndrome were sent home to perish without attempts at surgery, further limiting the collection of accurate retrospective data. It was therefore felt that it would prove impossible to study a relatively complete cohort of patients with true mitral atresia, when compared to the population of patients with the clinically and morphologically more distinct entities of tricuspid atresia and double inlet ventricle.

By limiting the survey to only patients who presented within the first year of life, the study has avoided undue bias towards patients with features that favoured survival. Many previous reports, particularly with respect to patients with double inlet ventricle, only examined older patients (Kawashima et al, 1976; McGoon et al, 1977; Gale et al, 1979; Feldt et al, 1981; Moodie et al, 1984a, 1984b; Stefanelli et al, 1984). The mean age of entry in one much quoted study of patients with double inlet ventricle from the Mayo Clinic, for instance, was 9.7 years for unoperated patients (Moodie et al, 1984b) and 9.6 years for those surgically palliated (Moodie et al, 1984a). In another, the median age for comparable palliative surgery was 22 months (Stefanelli et al, 1984). Similar older patient groups are found in several other surgical reports concerning patients with tricuspid atresia (Trusler and Williams, 1980; De Brux et al, 1983; Cleveland et al, 1984; Mair et al, 1990). Equally, limiting the upper age of entry into the study to one year of age, avoids the opposite extreme of considering only critically ill neonates.

Referral patterns to different institutions introduce a further unquantifiable bias in selection. During the period of study, the two hospitals involved were the primary referral centres for the majority of children with double inlet ventricle and tricuspid atresia in South East England. The population examined should therefore have suffered little bias from selection based on clinical or surgical criteria, or uncertain referral patterns. Indeed, given that nearly all patients with tricuspid atresia will initially present in infancy, the current cohort should represent a near complete postnatal record for this lesion. In addition, the time period of this study was during the 'modern' era when definitive surgery by a Fontan-type procedure had become the ultimate goal of initial management for the vast majority of both cohorts of patients, avoiding bias due to earlier 'survival at any cost' management strategies. However, the results do inevitably only reflect the medical practice at the two institutions during a specific time span (1972-1989) and this practice has evolved both during and after the period of study.

7.1.2 Statistical analysis

The impossibility of determining the true natural history without any form of intervention, from a group of patients who have usually undergone at least one operative procedure, is well recognised. This has been thoroughly discussed by others in reference to analysis by 'treatment received' rather than by intention to treat (Peto et al, 1977). However, because the number of patients receiving *definitive* operations was relatively small, the current analysis gives a reasonably accurate estimate of survival without (or before) definitive repair.

Important potential sources of bias were present due to the unavoidable individualisation of both the timing and form of therapy implemented. Also, the analyses did not take into account the clinical status of the patients prior to surgery (except when *in extremis* at initial presentation), or the evolving morphology of the underlying lesions, such as progressive closure of ventricular septal defects with time (Anderson et al, 1985; Rao, 1992d). Hence, the major assumption was made that the calculated relative risks remained both independent of any morphological changes that occurred during growth, and that they remained constant from the (arbitrary) time of initial presentation to the tertiary centres throughout subsequent follow-up. Furthermore, this was irrespective of palliative operative interventions and changes in surgical techniques and management strategies.

Despite these unquantifiable biases, the methods and the patient population in this study allow for the first time, an estimation of the fate of an individual infant with virtually any variant of double inlet ventricle or tricuspid atresia to be calculated, in terms of both survival and suitability for definitive repair. However, these patient-specific predictions are limited by the fact that it was not possible to derive confidence limits due to the use of a notional baseline patient as a reference.

7.1.3 Assessment of the merits of palliative surgery using risk factor analysis

The assessment of the effects of palliative operations on outcome presented particular analytic problems, as there was no control group and surgery was undertaken at differing times for unspecified and often unplanned reasons. There was also a danger that a death soon after an operation might be ascribed to the intervention itself, when it

could primarily be due to the underlying clinical condition and morphological feature that had prompted the operation. Furthermore, the extent to which statistical analyses can reconstruct the 'natural history' of patients with congenital heart disease (in other words, survival *without* palliative or definitive surgery) so as to act as a control, remains debatable. The reasons for this are, as stated above, consistent with those which make analyses of randomised trials by 'treatment received', rather than by 'intention to treat', subject to considerable bias (Peto et al, 1977). Patients who undergo palliative procedures may be different in some way from those with similar morphology who did not undergo such procedures. Simply deleting them by any physical or statistical manoeuvre increases the probability of error. Again, patient selection and the clinical status of the child prior to surgery add other potential and unquantifiable biases. Thus, the same assumption was made for this analysis as that above: that the relative risks following an operation were independent of the morphological factors either existing at initial presentation to the tertiary centres or at the time of operation.

Nevertheless, whilst taking these limitations into consideration, an analysis was attempted using data from the patients with double inlet ventricle to determine the possible benefits of palliative surgery. This was done using the technique of time-varying covariates (Cox and Oakes, 1985) to express the relative risks of the palliative procedure for the population who underwent such surgery, in comparison to the underlying risk of a morphologically similar 'control' group who did not undergo surgery. The latter risk estimate was obtained by stratification of the actuarial survival of this 'control' group, by means of the appropriate Cox coefficients.

Unfortunately, current statistical techniques did not have sufficient power to enable the calculation of predictions and comparisons specific for each patient, for later outcome with and without palliative operations.

Chapter 8

Discussion of morphology, overall patient survival and risk factor analyses

8.1 Patients with double inlet ventricle

8.1.1 Morphology

The relatively unselected nature of the population of patients with double inlet ventricle in this study led to a greater prevalence of lesions found to affect survival adversely than reported in series with an older age of entry. For example, only 11% of the total group of 167 patients reported by Moodie and associates (1984a, 1984b) had atrial isomerism, none had double inlet right ventricle and only 7% had pulmonary atresia. This is distinct from the proportions of 25%, 18% and 20% respectively, found in the patients in the current series. Stefanelli and colleagues (1984) did not report any patients with systemic outflow obstruction, whilst Moodie's group (1984a, 1984b) reported only 8% with an hypoplastic aortic arch or coarctation, in comparison to 18% with such obstructive lesions in the present group. In contrast, factors shown in the present analysis that favoured survival, such as pulmonary outflow stenosis, were correspondingly more common in both these series (64%, Moodie et al, 1984a, 1984b; and 51%, Stefanelli et al, 1984). Indeed, the beneficial effect that pulmonary stenosis conferred on the patients in the present series was not apparent in the Mayo Clinic cohort (Moodie et al, 1984b). This suggests that this benefit was only of significance during infancy when other high risk factors, such as systemic outflow obstruction and

pulmonary atresia were common, as such patients were unlikely to have survived long enough to have been referred to such quaternary centres.

The morphological spectrum of the current series resembles more closely that found at autopsy (Anderson et al, 1979) and in a small infant study (Chen et al, 1984), in which there were high proportions of associated lesions (atrial isomerism in 25% and systemic arterial obstruction in 30%).

8.1.2 Actuarial survival, risk factors and predicted survival

The preponderance of adverse morphological features meant that the outcome for the whole group of patients with double inlet ventricle in this study was predictably worse than in previous reports, with only a 40% survival at age five years and 35% at age ten years. Only 7% of the entire group the would be expected to survive without surgical intervention, to reach the mean age of entry (9.7 years) in the study of unoperated patients reported by Moodie et al (1984b). These results and the likely natural history are more similar to that of an historical series of paediatric necropsies from the era prior to palliative surgery. In this report, 87% of the 32 patients with "single ventricle" (excluding tricuspid atresia) had died in their first year; and all had died prior to five years of age (Samanek et al, 1988).

Multifactorial analysis with quantification of predicted survival provided a means of forecasting the likely outcome for the individual patient with double inlet ventricle with any combination of the variables given in Table 4-3 (page 89). Not surprisingly, patients with more complex lesions fared worse than those with balanced physiology

and few associated anomalies. Patients presenting in the first few weeks of life, particularly with acidosis, had a poor prognosis. This was partly because of the severity of the structural and functional cardiac abnormality inherent in these neonates at initial presentation, and partly due to the fact that many patients presented in the pre-prostaglandin era. These findings are consistent with the poor prognosis reported in other series which focused on patients with double inlet ventricle and specific adverse morphological features, such as atrial isomerism (Chiu et al, 1988; Phoon and Neill, 1994) or a common atrioventricular valve (Stein et al, 1990).

Patients with double inlet left ventricle, discordant ventriculo-arterial connections and balanced pulmonary blood flow had perhaps a surprisingly good prognosis for at least ten years (Figure 4.4, page 92). This was only marginally worse when pulmonary blood flow was reduced and palliative surgery was consequently needed. In contrast, those with the same anatomy but high pulmonary blood flow did not fare so well, with a predicted survival of only 60% at age ten years (Figure 4.5, page 93). This finding is most likely to reflect the presence of associated systemic outflow obstruction at various levels in this patient group (see Chapter 11, page 201).

8.2 Patients with tricuspid atresia

8.2.1 Morphology

As with the double inlet ventricle patients, the 'less selected' nature of the tricuspid atresia cohort meant that the incidence of the rarer and more adverse forms of the lesion, virtually unrepresented in previous large clinical series (Dick et al, 1975; Kyger

et al, 1975; Williams et al, 1976; Patel et al, 1978; Villani et al, 1979; Trusler and Williams, 1980; Cleveland et al, 1984; Girod et al, 1987; Fesslova et al, 1989; Tam et al, 1989; Mair et al, 1990; Dick and Rosenthal, 1992), was relatively high. In particular, obstruction to systemic outflow was far more common in the present series (15%) when compared to the above studies (0-9%), but was more similar to the 8% to 18% reported in three post-mortem series (Vlad, 1978; Weinberg, 1980; Scalia et al, 1984).

Of further interest was the finding that only a total of 23% of the patients with tricuspid atresia had a restrictive atrial communication at first assessment or during follow-up. This incidence is similar to that reported in a large autopsy series (Thoele et al, 1991) and supports the view that balloon atrial septostomy should be reserved for those with clinical or echocardiographic evidence of systemic venous obstruction (Dick et al, 1975; Thoele et al, 1991; Rao, 1992c). This differs from the experience of patients with mitral atresia, in whom interatrial restriction is common and progressive and usually requires transcatheter or surgical relief (Starc and Gersony, 1986).

8.2.2 Actuarial survival, risk factors and predicted survival

The ongoing poor fate of these patients with tricuspid atresia has only been hinted at in previous reports (De Brux et al, 1983; Tam et al, 1989; Thoele et al, 1991). Perhaps surprisingly therefore, the outcome for this whole group was only comparable to that of a previous generation of patients with tricuspid atresia who presented in the early, pre-Fontan era (Dick et al, 1975; Dick and Rosenthal, 1992). This equivalence of outcomes is attributable to the high incidence of adverse morphological features in the current series, as opposed to the relative lack of surgical and medical expertise of the 1970s and

earlier. Equally, the different cohorts involved indicate that direct comparisons should not be made between the outcome of the current series and the better fate reported for patients with tricuspid atresia who have undergone a Fontan operation (De Brux et al, 1983; Cleveland et al, 1984; Girod et al, 1987; Fesslova et al, 1989; Tam et al, 1989; Mair et al, 1990). Additionally, it can be noted that the worse outcome of males in one report (De Brux et al, 1983) is readily attributable to the higher incidence of discordant ventriculo-arterial connections in males, which in turn entails a high chance of having or acquiring systemic outflow obstruction and a consequent poor prognosis (see Chapter 6, page 156).

Multifactorial analysis with quantification of predicted survival provided a means of forecasting future survival for the individual patient with tricuspid atresia, using any combination of variables given in Table 5-3 (page 133). The predictive curves clearly exemplify the highly variable outcome of infants presenting with tricuspid atresia. As with double inlet ventricle patients, those with few associated lesions are likely to fare remarkably well, at least up to ten years of age (Figures 5.3 and 5.4; pages 136, 137). Similarly and as expected, the more complex the associated features present at initial assessment, the worse the predicted outcome.

8.3 Morphological comparisons between patients with double inlet ventricle and those with tricuspid atresia

There were clear morphological distinctions between the two lesions. Those with tricuspid atresia nearly always had the usual atrial arrangement and a dominant left ventricle, whereas 25% of patients with double inlet ventricle had isomerism of the atrial appendages (visceral heterotaxy or asplenia / polysplenia syndrome) and nearly 30% had a dominant ventricle of either right or indeterminate morphology. Unsurprisingly, the presence of abnormal pulmonary venous connections in patients with double inlet ventricle was highly associated with right atrial isomerism and was correspondingly very rare in the tricuspid atresia cohort. Evidently, a common atrioventricular valve is only likely to be present in those with double inlet ventricle. This was found in just one patient in the tricuspid atresia group, in the context of partitioned orifices and an imperforate right atrioventricular valve, with atrioventricular concordance and right atrial isomerism.

The respective ventriculo-arterial connections were also dissimilar. Two thirds of the cohort with tricuspid atresia had concordant ventriculo-arterial connections (with or without effective pulmonary atresia), whilst only 10% had a similar arrangement in the group with double inlet ventricle, the eponymous 'Holmes heart' (1824). This is partially explained by the high incidence of non-left ventricular dominance in the double inlet cohort. Hearts with double inlet to a dominant ventricle of right or indeterminate morphology usually had double outlet ventriculo-arterial connections. However, even examining only the anatomy of those patients with a dominant left ventricle demonstrated that nearly two thirds of hearts with double inlet left ventricle

had discordant ventriculo-arterial connections, compared to only 25% of those with tricuspid atresia. Despite this, the proportions of infants with systemic outflow obstruction, which occurred almost exclusively in the setting of discordant ventriculo-arterial connections, were similar between the two groups at 16% to 18%.

8.4 The additive indices

For ease of clinical use, the additive indices were calculated for both patient groups (Tables 4-4 and 5-4; pages 95, 138). These proved to have comparable predictive power to the more laborious multivariate analysis derived, survival curve method. It allowed the rapid prediction of outcome with respect to survival, palliative interventions and suitability for a future Fontan-type procedure (for tricuspid atresia patients), based on the fate of the current two patient cohorts (Tables 4-5, 5-5 and 5-10; pages 96, 139, 155). The index for patients with double inlet ventricle was also found to be robust to the addition of palliative surgical risk factors, with only minor changes in the resultant scores. The clinician should therefore be able to use these indices and cross-tabulations of expected patient outcome with confidence, when considering proposed treatment regimens with parents of newly diagnosed infants with double inlet ventricle or tricuspid atresia. This is discussed further in Chapter 12 (page 213).

Chapter 9

Discussion of the results and merits of palliative surgery

9.1 Operative mortality after palliative surgery

The particularly poor natural history for unoperated patients with tricuspid atresia (Dick et al, 1975; Williams et al, 1976) reflects the high incidence of severe obstruction to pulmonary and systemic outflows. These mandate early surgical intervention in over 90% of patients if they are to survive (Dick et al, 1975; Williams et al, 1976; Vlad, 1978; Tam et al, 1989). Although patients with double inlet ventricle usually have more complex anatomy (Franklin et al, 1991), a larger number of this cohort may present at over one year of age, due to the higher proportion with a more balanced physiology in infancy. Many patients with double inlet ventricle will therefore not require palliative surgery until a much older age than those with tricuspid atresia (Moodie et al, 1984a; Stefanelli et al, 1984; Franklin et al, 1991b, 1993). The risks of surgery are known to be higher in infancy than in older children (Stark et al, 1980; Castaneda et al, 1989). Survival after initial palliative surgery in the current series was similar to results from other series involving infants (Dick et al, 1975; Williams et al, 1976; Villani et al, 1979; Trusler and Williams, 1980; De Brux et al, 1983; Chen et al, 1984; Cleveland et al, 1984; Sapire et al, 1986; Crupi et al, 1987; Mair et al, 1990), and worse than results in older children, who presented at an older age with double inlet ventricle (Moodie et al, 1984a; Stefanelli et al, 1984). Stefanelli and associates (1984) reported an 85% actuarial survival at ten years post-surgery for those patients undergoing construction of

systemic-to-pulmonary arterial shunts, compared to 56% at eight years post-surgery in the present study. Less than 10% of the 121 patients palliated in the current group however, were older at operation than the median age at surgery of 22 months in the series of 116 patients reported by Stefanelli and colleagues (1984).

It is of interest that the fate of patients who underwent isolated banding of the pulmonary trunk was no worse than that of patients who underwent construction of a systemic-to-pulmonary arterial shunt, regardless of the ventriculo-arterial connections (Figures 4.7 and 5.5; pages 100, 143). This contrasts with the experience of Freedom's group (1986), although their report omits details of the presence of aortic arch obstruction and its relationship to subsequent subaortic stenosis and survival. The dismal fate of those requiring additional aortic arch repair in this series has caused the two institutions in the present study and others, to change to more aggressive initial management of these infants (Franklin et al, 1990; Karl et al, 1991; Di Donato et al, 1993). This is discussed further in Chapter 11 (page 201).

The higher operative mortality and incidence of later pulmonary arterial distortion in patients whose pulmonary blood flow was augmented by procedures other than a Blalock-Taussig systemic-to-pulmonary arterial shunt, has led most units, including the hospitals in the present study, to largely abandon these alternative procedures (Mietus-Snyder et al, 1987; Mair et al, 1991; Rao, 1992e; Franklin et al, 1993).

9.2 Assessing the benefits of palliative surgery

This analysis was restricted to those patients with double inlet ventricle. It established that, despite a relatively high early mortality in the first post-operative month, the infants who survived the palliative procedure benefited in the medium term, when compared to those still alive but not submitted to such surgery. In contrast, Moodie and associates (1984a) have shown that in older patients (already selected by their survival), palliative surgery did not significantly enhance long term survival. This suggests that palliative operations enable patients to reach an age when definitive procedures are currently undertaken, but they do not ensure long term survival. Care must be taken however, in drawing such conclusions, as neither study was randomised and the suitability for later definitive surgery was not addressed in these analyses.

It was notable that patients who underwent banding of the pulmonary trunk, with and without relief of aortic arch obstruction, did not appear to show benefit from palliation, even in the medium term. This was due to the subsequent early and usually fatal development of subaortic stenosis in many of these patients, particularly those who required surgery to the aortic arch (Franklin et al, 1990). It is argued in Chapter 11 (page 206) that this form of palliation is inappropriate for many of these patients. This further emphasises that this analysis must be interpreted with caution, as only factors detected at initial assessment were used. It was erroneously assumed in this specific case, that these factors remained of constant relative importance throughout follow-up, as discussed in Chapter 7 (page 176). In other words, the analysis did not consider new adverse events that developed after palliation, but which were nevertheless related to

the underlying pathology, such as the development of new subaortic stenosis or pulmonary arterial distortion, and which subsequently might profoundly affect survival.

9.3 The long term outlook after palliative surgery

Reports of the long term outcome after conventional palliative surgery alone in patients with tricuspid atresia or double inlet ventricle, range from an actuarial survival of 45% to 84% at ten years of age (Taussig et al, 1973; Dick et al, 1975; Taussig, 1976; Williams et al, 1976; Trusler and Williams, 1980; De Brux et al, 1983; Moodie et al, 1984a; Stefanelli et al, 1984; Dick and Rosenthal, 1992) to only 32% to 55% survival at age twenty years (Taussig et al, 1973; Dick et al, 1975; Taussig, 1976; Dick and Rosenthal, 1992). These reports generally examined the fate of less complex anatomical variants of these lesions and an even more dismal outlook can be expected for those with more complex pathology, even in the 1990s (Kuroda et al, 1987; Moak and Gersony, 1987; Stein et al, 1990; Phoon and Neill, 1994; Sadiq et al, 1996), as confirmed in the present study (Franklin et al, 1991a, 1991b, 1993). In addition, there are reports of a progressive decrease in exercise performance in those who have survived into adolescence (Driscoll et al, 1984; Akagi et al, 1991). This is corroborated by evidence of deteriorating atrioventricular valve function and myocardial performance with increasing age in similarly palliated patients (LaCorte et al, 1975; Kuroda et al, 1987; Moak and Gersony, 1987; Akagi et al, 1991; Sluysmans et al, 1992).

Not surprisingly given these data, most centres since the 1970s have turned to the various modifications of the Fontan operation as the definitive surgical option for patients with tricuspid atresia and double inlet ventricle. Although there are numerous reports of the benefits of such surgery, increasingly there are also publications detailing the longer term problems after Fontan-type procedures, as discussed in the next Chapter (page 191). Unfortunately, a controlled trial of definitive surgery versus purely palliative therapy was never undertaken, and in the current era such a study would raise major ethical objections.

Chapter 10

Discussion of the results and merits of definitive surgery

10.1 The benefits and hazards of Fontan-type definitive surgery

The medium term results after modified Fontan procedures undertaken in the late 1970s and early 1980s for patients with double inlet ventricle or tricuspid atresia have been encouraging (Kirklin et al, 1986; Fontan et al, 1990; Mair et al, 1990, 1991), with improvements in left ventricular myocardial performance (Gewillig et al, 1990b; Sluysmans et al, 1992), exercise capacity (Zwellers et al, 1989; Gewillig et al, 1990a) and functional status (Mair et al, 1992). Recent reports however, have also highlighted the longer term problems of a deterioration in functional capacity, arrhythmias, hepatic dysfunction and protein-losing enteropathy in many of the patients operated on in the early and mid-Fontan era (Fontan et al, 1990; Cohen et al, 1991; Cromme-Dijkhuis et al, 1993; Driscoll et al, 1992, Feldt et al, 1996). Those who fared worst in these reports had heart lesions other than tricuspid atresia, a dominant ventricle other than a left ventricle, an early operation date, poor pre-operative functional status and a prolonged post-operative course. Poor outcome also correlated with adverse pre-operative haemodynamics and cardiac status, particularly raised pulmonary arterial pressure, atrioventricular valvar regurgitation, dominant ventricular hypertrophy and dominant ventricular dysfunction.

Another major long term concern has been the development of pulmonary arteriovenous fistulae, as previously reported for patients with non-pulsatile pulmonary flow after a classical Glenn operation, i.e. a superior unidirectional cavopulmonary anastomosis (Mcfaul et al, 1977; Kopf et al, 1990). Recent reports have shown that this cause of late clinical desaturation is a particular problem in those patients with left atrial isomerism in whom there is an azygous or hemi-azygous continuation of the inferior caval vein to a left or right superior caval vein (Moore et al, 1989; Bernstein et al, 1995; Srivastava et al, 1995). This anatomy allows a near total cavopulmonary connection to be created by simply performing a unilateral (or bilateral if there are bilateral superior caval veins) superior cavopulmonary anastomosis (Humes et al, 1988). This results in the entire systemic venous return flowing to the pulmonary arteries, except for the hepatic and coronary sinus venous returns, which continue to drain anomalously into the neo-pulmonary venous atriums. Srivastava and colleagues (1995) have shown that it appears to be the lack of an 'hepatic factor' in these patients that causes them to develop pulmonary arteriovenous fistulae, as further surgery to channel the hepatic venous return to the lungs has reversed this pathology in some cases. Although this hepatic factor has yet to be identified, these findings have major implications for all patients for whom a Fontan-type procedure would be the optimal definitive surgical option. It supports the concept of leaving additional sources of pulmonary blood flow patent when constructing a bidirectional cavopulmonary anastomosis (Glenn procedure), in patients where this serves as a staging procedure to definitive palliation by a total cavopulmonary connection (see Chapter 12; page 218). It also supports the trend towards an earlier age of completion of the total cavopulmonary connection, to ensure adequate hepatic venous return to the pulmonary vascular bed. Furthermore, the construction of a specific hepatic venous conduit to the lungs for

those patients with left atrial isomerism would appear to be mandatory. Despite these potential remedies, there remains concern about future pulmonary sequelae, as abnormal pulmonary venous flow patterns have been documented in patients without atrial isomerism (Cloutier et al, 1985) and they may be a factor in the progressive, exercise induced, systemic desaturation seen in some patients (Nir et al, 1993). It is also important however, to exclude other less sinister causes of systemic desaturation, such as systemic to hepatic venous collaterals in patients with left atrial isomerism (Stümper et al, 1995), or right to left interatrial communications in patients who do not have an isomeric syndrome (Hsu et al, 1995).

To address the problems of higher operative mortality in those with the most complex lesions and the above longer term concerns, the last decade has witnessed considerable modifications in surgical technique, such as the total cavopulmonary connection (de Leval et al, 1988; Stein et al, 1991), atrial baffle fenestration (Bridges et al, 1990b) and the use of extracardiac conduits to channel inferior caval flow directly to the pulmonary arteries and so avoid atrial surgery altogether (Humes et al, 1988; Marcelletti et al, 1990). Many centres have concurrently begun to stage the definitive operation in order to deal with adverse lesions such as subaortic stenosis (Cheung et al, 1990; O'Leary et al, 1992; Di Donato et al, 1993) or pulmonary arterial distortion (Pridjian et al, 1993), prior to full definitive repair. This approach is often combined with the creation of a bidirectional superior cavopulmonary (Glenn) anastomosis (see Chapter 12; page 218). There is already some evidence that these methods are improving both short and long term morbidity and mortality (Rothman et al, 1987; Bridges et al, 1990a, 1990b; Balaji et al, 1991; Gelatt et al, 1991; Jacobs and Norwood, 1994; Rosenthal et al, 1995). Nevertheless, the long term fate of the patients undergoing Fontan-type operations in

the current era, without the use of valved conduits and using strict selection criteria remains unknown, but is likely to be better than that for patients whose surgery was undertaken in the early Fontan era (Driscoll et al, 1992; Cetta et al, 1996). This is particularly relevant for patients with sub-optimal anatomy, such as those with a dominant right ventricle (Matsuda et al, 1987; Akagi et al 1993). Thus, despite the above reservations, management in infancy in the mid 1990s continues to aim to ensure survival, whilst establishing and maintaining suitable anatomy and physiology for a subsequent Fontan-type procedure.

10.2 Suitability for a Fontan-type operation and the use of palliative surgery

Surgical experience and technical modifications have shown that the Fontan principle can successfully be applied to most *morphological* variants of tricuspid atresia, double inlet ventricle and other functionally univentricular hearts, such as the hypoplastic left heart syndrome (Marcelletti et al, 1980; Hopkins et al, 1985; Mayer et al, 1986; Danielson, 1987; Puga et al, 1987; Matsuda et al, 1987; Humes et al, 1988; de Leval et al, 1988; Bridges et al, 1990a, 1990b; O'Leary et al, 1992; Jacobs and Norwood, 1994). Although the *physiological* requirements are demanding, patients who do not fulfil all ten criteria of Choussat and colleagues (1978) may survive the operation (Alboliras et al, 1985; Kirklin et al, 1986; Mayer et al, 1986; Danielson, 1987; Balaji et al, 1991; Serraf et al, 1994). However, several studies have reported an incremental increase in operative risk in such patients that is proportional to the number of 'rules' which are broken (Pacifico, 1986; Humes et al, 1987; Bridges et al, 1990b, Balaji et al, 1991).

Survival may also be at the cost of a subsequent relatively reduced exercise performance (Gewillig et al, 1990a) and a higher incidence of arrhythmias (Gewillig et al, 1992), when compared to patients with few adverse features. It is therefore difficult to define absolute guidelines for suitability for a Fontan-type operation (Kirklin et al, 1986; Mayer et al, 1986; Humes et al, 1987; Serraf et al, 1994). The criteria used in this study inevitably represent a compromise. Even using the relatively flexible criteria of the present study, 11% to 17% of the two cohorts were considered retrospectively to have been unsuitable at initial assessment at the tertiary centres for a future Fontan-type procedure and a further 3% to 12% were deemed potentially unsuitable because of the presence of very complex anatomy.

Although most patients in this study who required palliative surgery received it, there remained a dilemma as to how best to manage those infants with haemodynamically severe, often multiple associated lesions. Throughout the study, the decision as to whether or not to undertake surgery was arbitrary. It could be argued that surgery should have been attempted in more of these, often critically sick patients. When surgery was performed however, the outcome proved no better than in those who did not undergo such surgery, but who had similar anatomy (Tables 4-9 and 5-8, pages 107, 147). Recent and future surgical advances (Vargas et al, 1987; Okita et al, 1989; Cheung et al, 1990; Karl et al, 1991; Laks et al, 1992), as well as the use of staged palliation for complex lesions (Bridges et al, 1990a, 1990b; Di Donato et al, 1993; Jacobs and Norwood, 1994, Sadiq et al, 1996), will undoubtedly continue to influence these criteria for Fontan suitability. Nonetheless, significant proportions of patients, particularly with double inlet ventricle and atrial isomerism, are still currently unsuitable for more conventional operative intervention in isolation. Palliation using

higher risk, more complex procedures is increasingly being undertaken in many of these patients with particularly difficult anatomy, but at present the results remain less favourable (Sadiq et al, 1996).

Although 86% of patients with tricuspid atresia and 71% of those with double inlet ventricle were considered on retrospective review to be potentially suitable at initial assessment for a Fontan-type procedure, by four years of age well over 40% of these had either died or had developed adverse features that precluded a relatively low risk definitive operation. In fact, most patients died either at or prior to palliative surgery. This early mortality has been, and will continue to be, reduced by improvements in early diagnosis (Finley et al, 1989; Franklin et al, 1991d; Allan et al, 1994), medical management (such as the use of prostaglandin since 1980) and surgical techniques.

Despite efforts aimed at closer follow-up and better treatment of infections, there is still likely to remain a group of patients who die suddenly and unexpectedly (9%-10% of the patients in this series). This is a well recognised yet under-reported phenomenon in children with congenital heart lesions (Liberthson, 1996). The present report is the first to identify this as a particular problem in patients with double inlet ventricle or tricuspid atresia. Sudden death has been associated with a late age of definitive repair in patients with other complex congenital heart lesions (Deanfield et al, 1983; Shen et al, 1990), including after the Fontan operation (Fontan et al, 1990). It has also been linked with myocardial degeneration (Jones et al, 1977), fibrosis (Hegerty et al, 1988; Weber et al, 1993) and arrhythmias (Deanfield et al, 1983). Other potentially important factors in these patients are the profoundly abnormal cardiac structure, chronic dominant ventricular pressure and/or volume overload, and varying degrees of chronic hypoxia.

The relationship of these multiple factors to the incidence of sudden death in the younger patients in the current report remains unclear and requires further study. Of interest are two recent reports documenting increased fibrosis, compared to normal controls, in patients with tricuspid atresia (Ho et al, 1996) and aortic valve atresia (Schwartz et al, 1996). In both papers the authors document an increase in myocardial collagen with age. In the tricuspid atresia patients even the neonates had higher levels of fibrosis compared to the normal hearts examined, whilst in those with aortic atresia, perhaps unexpectedly, the newborns examined had a normal myocardial volume fraction of collagen. These studies may also support the promotion of earlier definitive surgery (see Chapter 12, page 214).

New adverse features became evident in 13% to 16% of the patients, mostly in the first four years of life. The most common of these were subaortic stenosis and pulmonary arterial distortion. Subaortic stenosis developed only in those with a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow. Management of this group remains difficult and is discussed in detail in Chapter 11 (page 201).

Pulmonary arterial distortion increases the risks of Fontan-type surgery, sometimes to prohibitive levels (Mayer et al, 1986; Fontan et al, 1990; Driscoll et al, 1992). This emphasises the need for scrupulous surgical technique during palliative operations, as well as the avoidance of non-Blalock-Taussig and multiple shunt procedures (Kirklin et al, 1986; Mietus-Snyder et al, 1987; Rao, 1992e). A complicating factor is recent evidence documenting late acquired pulmonary arterial discontinuity in patients with tricuspid atresia and right atrial isomerism (Waldman et al, 1996). This was unrelated to

previous systemic-to-pulmonary arterial shunt surgery and was documented as not being present at initial assessment. It appears to be due to an abnormal extension of arterial ductal tissue onto the pulmonary arteries. Clearly, recent angiography remains necessary before any form of definitive surgery is attempted.

In contrast, atrioventricular valvar regurgitation and dominant ventricular dysfunction developed relatively infrequently during follow-up in the current series. This may be a consequence of the younger age of the patients compared to those in previous studies, as these complications are known to increase with age and following additional palliative procedures (LaCorte et al, 1975; Kirklin et al, 1986; Mayer et al, 1986; Pacifico, 1986; Kuroda et al, 1987; Moak and Gersony, 1987; Stein et al, 1990; Uemura et al, 1995c).

Several patients with relatively unobstructed pulmonary blood flow at initial assessment went on to develop irreversible pulmonary vascular disease during follow-up due to inadequate palliation in infancy. They presented early in the experience of the two tertiary hospitals with relatively few symptoms. It is now clear that aggressive early palliation to restrict pulmonary blood flow in such patients is mandatory, so as to prevent the incipient development of pulmonary vascular disease (Juaneda and Haworth, 1984, 1985). The avoidance of Waterston and Potts systemic-to-pulmonary arterial shunt procedures is also advisable, as they may cause unilateral high pulmonary blood flow and subsequent pulmonary vascular damage, as well as pulmonary arterial distortion (Rao, 1992e).

10.3 Definitive surgery by means of a ventricular septation operation

At first sight ventricular septation appears the most attractive definitive intervention for patients with double inlet ventricle, as it creates a biventricular circulation with less stringent physiological requirements. However, surgical experience has shown that it can be performed with low operative mortality (up to 17%) only in a highly selected subgroup of patients (Ebert, 1984; Stefanelli et al, 1984; Bargeron, 1987; Kurosawa et al, 1990). In this study the narrow criteria required for success were present in only 23% of the patients at initial assessment. This is similar to an autopsy study, where only five out of 41 patients had suitable anatomy for a 'simple' septation procedure (Girod et al, 1984; Quaegebeur et al, 1987). The attractiveness of ventricular septation is diminished further by the high incidence (33% - 88%) of post-operative complete heart block requiring permanent pacing (Stefanelli et al, 1984; Pacifico, 1986), although more recent surgical methods appear to have reduced the frequency of this complication (Ebert, 1984; Kurosawa, 1990; Bogers et al, 1992).

The application of this approach for patients potentially suitable for both definitive surgical options will ultimately depend upon the results at long term follow-up, especially in those with borderline pulmonary arteriolar resistance, who appear to have an inferior functional result after Fontan-type surgery (Gewillig et al, 1990a). Currently, the practice for patients with double inlet ventricle at the tertiary hospitals in the present study, as in most other institutions, is generally to favour a Fontan-type procedure, usually a total cavopulmonary connection, in preference to a ventricular septation operation. The ventricular septation procedure is considered for those few

patients with suitable anatomy and a modestly elevated pulmonary arteriolar resistance (2 to 6 units.m^2), which precludes a low risk Fontan-type procedure.

Chapter 11

Discussion of the study on subaortic stenosis

Subaortic stenosis in patients with double inlet ventricle or tricuspid atresia occurs almost exclusively in those with the morphological substrate of a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow (Figure 1.1, page 31). Systemic blood flow must leave the left ventricle by way of a ventricular septal defect in order to reach the rudimentary right ventricle and from there enter the aorta. The ventricular septal defect is usually entirely muscle bound and as such, potentially restrictive (Anderson et al, 1985; Rao, 1992d). As outlined in Chapter 1 (page 30), pulmonary blood flow must be reduced in early infancy to ensure a low pulmonary arteriolar resistance prior to a Fontan-type procedure (Choussat et al, 1978; Kirklin et al, 1986; Juaneda and Haworth, 1984, 1985). Simple banding of the pulmonary trunk may promote ventricular hypertrophy (Kirklin et al, 1986; Seliem et al, 1989; Cohen et al, 1991) and accelerate the natural tendency of the ventricular septal defect to close (Mesko et al, 1973; Freedom et al, 1986; Rao, 1992d), resulting in subaortic stenosis and higher risk definitive surgery (Kirklin et al, 1986; Pacifico, 1986; Cohen et al, 1991; Penny et al, 1992; Cortes et al, 1994). Consequently, the place of this conventional approach has been brought into question for virtually all such patients, despite the relatively high initial operative mortality of alternative surgical approaches (Freedom, 1987; Rothman et al, 1987). This study was undertaken to

determine optimal management strategies for these patients and to establish guidelines to help distinguish those at particular risk of developing subaortic stenosis.

11.1 Previous studies and patient selection

Patients with a dominant left ventricle, discordant ventriculo-arterial connections and unobstructed pulmonary blood flow represent approximately 30% of patients with double inlet ventricle and 20% of those with tricuspid atresia who are initially seen at tertiary institutions in the first year of life. Aortic arch obstructive lesions will be present in approximately 50% of these infants. The proportions of patients potentially at risk of subaortic stenosis have been reported in autopsy series (Freedom et al, 1977; Vlad, 1978; Weinberg, 1980; Girod et al, 1984; Scalia et al, 1984), but rarely in clinical studies. Most clinical series have only examined patients of an older age (Moodie et al, 1984a, 1984b), or have been limited to patients who have either undergone palliative operations (Williams et al, 1976; De Brux et al, 1983; Cleveland et al, 1984; Stefanelli et al, 1984; Freedom et al, 1986; Jacobs et al, 1995; Jensen et al, 1996) or definitive surgery (Feldt et al, 1981; DeLeon et al, 1986; Kirklin et al, 1986; Mayer et al, 1986; Coles et al, 1987; Danielson, 1987; Humes et al, 1987; Mair et al, 1990; Malcic et al, 1992). This inevitably means that the populations studied have been biased towards those with features that favour survival and have included few patients at risk of the early development of subaortic stenosis (Williams et al, 1976; De Brux et al, 1983; Cleveland et al, 1984; DeLeon et al, 1986; Mair et al, 1990; Malcic et al, 1992). Other reports have only focused on patients who have undergone surgery for established subaortic stenosis (Barber et al, 1984; Penkoske et al, 1984; DeLeon et al, 1986; Lin et

al, 1986; Newfeld et al, 1987; Rothman et al, 1987; Waldman et al, 1988; Di Donato et al, 1989, 1993; Ilbawi et al, 1991; Karl et al, 1991; Rychik et al, 1991; Lacour-Gayet et al, 1992; O'Leary et al, 1992; Webber et al, 1992; Gates et al, 1993; Huddleston et al, 1993; Lui et al, 1993; Carter et al, 1994; Brawn et al, 1995; Bu'lock et al, 1995; van Son et al, 1995), have been limited by very small numbers (Marcano et al, 1969; Gypes et al, 1970; Chen et al, 1984; Rao, 1992d), or have reported patient outcome in the pre-Fontan era (Dick et al, 1975; Patel et al, 1978). Furthermore, many of these studies do not give details of the ventriculo-arterial connections when describing patients palliated by banding of the pulmonary trunk (Cleveland et al, 1984; Moodie et al, 1984a, Stefanelli et al, 1984; DeLeon et al, 1986; Mayer et al, 1986; Humes et al, 1987; Mair et al, 1990), limiting comparison with the present study.

11.2 Subaortic stenosis at initial presentation

Subaortic stenosis was already present in 28% of the 102 patients when first assessed at the tertiary centres and 61% of these infants had a coexistent aortic arch lesion. These proportions are in accord with several autopsy series, where 10% to 50% of patients had subaortic stenosis (Vlad, 1978; Weinberg, 1980; Girod et al, 1984; Anderson et al, 1985), whilst 44% to 78% of such cases had associated aortic arch obstruction (Garcia et al, 1974; Scalia et al, 1984). They are also consistent with several surgical series of patients with either primary or acquired subaortic stenosis where 31% to 100% of cases are documented as having obstructive aortic arch lesions (Penkoske et al, 1984; DeLeon et al, 1986; Rothman et al, 1987; Karl et al, 1991; Rychik et al, 1991; Lacour-Gayet et

al, 1992; Matitiau et al, 1992; Webber et al, 1992; Gates et al, 1993; Huddleston et al, 1993; Brawn et al, 1995; Bu'lock et al, 1995; van Son et al, 1995; Jensen et al, 1996).

11.3 Acquired subaortic stenosis

This study has shown that, in the presence of aortic arch obstruction, subaortic stenosis inevitably developed after palliation by banding of the pulmonary trunk together with aortic arch repair. All of the patients in this series who had aortic arch obstruction but who did not have subaortic stenosis at initial assessment at the tertiary centres either developed subaortic stenosis by three years of age or died prior to this age. In contrast, the incidence of acquired subaortic stenosis after conventional palliation by banding the pulmonary trunk in patients without aortic arch obstruction was much lower, over a mean follow-up period of 8.5 years. This difference is consistent with the autopsy series of Scalia and colleagues (1984), in which subaortic stenosis developed only in hearts with associated coarctation of the aorta. It is difficult to compare these data directly with those of Freedom and associates (1986), who reported that 84% of their patients developed subaortic stenosis following banding of the pulmonary trunk, as the paper omits any reference to associated abnormalities of the aortic arch. In their later publication detailing 84 consecutive patients with tricuspid atresia, there appear to have been no patients with subaortic stenosis *de novo* (Tam et al, 1989). Furthermore, it was still not possible from the data provided to tease out which of the patients with acquired ventricular septal defect restriction, also had an aortic arch lesion at initial presentation. A recent series from Jensen and colleagues (1996) of 26 similar patients does confirm the findings of the present study, in that all eight patients who required aortic arch

surgery in addition to banding of the pulmonary trunk went on to develop subaortic stenosis in the months following their operation.

The reasons why these infants with aortic arch obstruction invariably and rapidly went on to acquire subaortic stenosis are not clear. Long term follow-up of patients who have undergone successful repair of uncomplicated aortic coarctation has shown that left ventricular hypertrophy often persists along with increased indexed left ventricular mass compared to normal controls (Carpenter et al, 1985; Krogmann et al, 1993; Kimball et al, 1994). These results correlated with enhanced systolic left ventricular performance, as shown by a raised shortening fraction and enhanced myocardial contractility, as well as reduced end-systolic wall stress (afterload). These findings were accentuated with exercise and corresponded with significant increases in Doppler derived pressure gradients over the site of the arch repair, without there being evidence of a true recurrent aortic coarctation (Carpenter et al, 1985; Kimball et al, 1994). The persistent hypertrophy may be sufficiently significant to cause impairment of diastolic function (Krogmann et al, 1993). It is speculated that these myocardial abnormalities may be due to such unresolved descending aorta gradients, as well as a chronic state of raised catecholamine production (Carpenter et al, 1985; Engle, 1985; Kimball et al, 1994). Both would lead to persistent levels of ventricular hypertrophy, which would be progressive in the setting of a further pressure load on the ventricle, such as a banded pulmonary trunk in a heart with discordant ventriculo-arterial connections. It is tempting to postulate that some or all of these factors have contributed significantly to the rapid narrowing of the ventricular septal defects in the current patient cohort, over and above the natural tendency for the septal defects to become smaller with normal growth.

In those infants without aortic arch obstruction, the size of the ventricular septal defect was a useful predictor for the development of subaortic stenosis after banding of the pulmonary trunk. The current data suggests that patients in whom the ventricular septal defect to ascending aorta ratio at initial assessment is less than 0.8, will have a high probability of acquiring subaortic stenosis after isolated banding of the pulmonary trunk. In contrast, this appears to be unlikely in those with a ratio that exceeds 1.0 (Franklin et al, 1990). These findings were corroborated by Matitiau and colleagues in 1992, when measuring the area of the ventricular septal defect in 28 similar patients, using a more complex methodology. They showed that those with an area of less than 2 cm^2/m^2 (indexed for body surface area) were at high risk of developing subaortic stenosis, whilst those whose area was over 3 cm^2/m^2 were very unlikely to do so, although the follow-up duration of their study was limited to between two and five years. Interestingly, in contrast to the present findings, nearly all of their patients with aortic arch obstruction also had relatively small ventricular septal defects.

11.4 Implications for optimal palliation

Infants who already have subaortic stenosis at initial presentation clearly require aggressive palliation. Unfortunately the reports of surgery in infancy continue to highlight the significant operative mortality for all surgical options (Table 11-1). The actual procedure used to relieve the subaortic narrowing will depend upon the experience of the individual surgeon. The most recent series, from surgery undertaken in the 1990s, are reporting mortality figures of less than 20% for most of the approaches listed in Table 11-1.

One of the most popular surgical options for these infants consists of a primary transection of the pulmonary trunk, followed by an anastomosis of the proximal pulmonary trunk to the ascending aorta together with the construction of a small systemic-to-pulmonary arterial shunt, in either a Damus-Kaye-Stansel fashion (DeLeon et al, 1986; Lin et al, 1986; Rothman et al, 1987; Waldman et al, 1988; Gates et al, 1993; Huddleston et al, 1993; Lui et al, 1993; Brawn et al, 1995; van Son et al, 1995), or as originally described by Norwood and colleagues in 1983. In the latter case the pulmonary trunk is also used to help relieve any hypoplasia or obstruction of the aortic arch (Rychik et al, 1991; Bu'lock et al, 1995). Recent surgical series have also shown better results for the Damus-Kaye-Stansel type approach in older patients (Gates et al, 1993; Huddleston et al, 1993; Lui et al, 1993; Carter et al, 1994; Jensen et al, 1996). There remains a concern however, about later significant semilunar valve regurgitation, which can occur in up to 50% of such patients (DeLeon et al, 1986), although technical modifications may minimise this in the future (Laks et al, 1992; Carter et al, 1994).

Table 11-1. Reports of surgery to relieve subaortic stenosis in infants

Procedure	Patients	Operative Deaths
Procedures after initial banding of the pulmonary trunk and aortic arch repair		
Left ventricle to descending aorta conduit	2	2 (100%)
Enlargement of VSD	2	0 (0%)
Ascending aorta to pulmonary trunk anastomosis and SPS shunt †	13	8 (61%)
Ascending aorta to pulmonary trunk anastomosis and Glenn shunt †	4	0 (0%)
Arterial switch ± SPS shunt	2	1 (50%)
Procedures after initial isolated banding of pulmonary trunk		
Enlargement of VSD	1	0 (0%)
Ascending aorta to pulmonary trunk anastomosis and SPS shunt †	6	1 (17%)
Primary procedures		
Pulmonary trunk to descending aorta conduit with arch repair & banding of the pulmonary trunk	1 ‡	0 (0%)
Ascending aorta to pulmonary trunk anastomosis ± arch repair and SPS shunt †	35	10 (29%)
Pulmonary trunk & aorta reconstruction ± arch repair and SPS shunt (Norwood-type procedure)	30 **[5]**	5 (17%)
Arterial switch with arch repair ± SPS shunt or banding of the pulmonary trunk	10	2 (20%)
Enlargement of VSD ± arch repair	1	0 (0%)

† Damus-Kaye-Stansel type procedure. ‡ Late death at age five months due to poor coronary perfusion.

Squared parentheses indicate the number of patients in whom no subaortic stenosis was evident at the time of surgery. SPS, systemic-to-pulmonary arterial; VSD, ventricular septal defect.

Cumulative data from the present study and references: Penkoske et al, 1984; DeLeon et al, 1986; Lin et al, 1986; Newfeld and Nikaidoh, 1987; Rothman et al, 1987; Waldman et al, 1988; Ilbawi et al, 1991; Karl et al, 1991; Rychik et al, 1991; Lacour-Gayet et al, 1992; Matitiau et al, 1992; Webber et al, 1992; Gates et al, 1993; Lui et al, 1993; Brawn et al, 1995; Bu'lock et al, 1995; van Son et al, 1995.

A recent favourable alternative has been the use of an arterial switch procedure together with aortic arch repair and the construction of a systemic-to-pulmonary arterial shunt as appropriate (Karl et al, 1991; Lacour-Gayet et al, 1992). The main drawbacks voiced for this approach are its technical demands and the difficulty in judging whether an accompanying shunt to augment pulmonary blood flow is needed. There are also long term concerns that apply to the arterial switch procedure which are relevant, such as the fate of the translocated coronary arteries and the development of supravalvar aortic stenosis (Freedom and Trusler, 1991). Evidently, concerns about supravalvar pulmonary stenosis will be abrogated by later Fontan-type definitive surgery.

The third surgical option put forward for these patients is direct enlargement of the ventricular septal defect, with or without right ventricular outflow tract patching. Avoidance of the conduction tissue when enlarging the septal defect is evidently important, but is not usually a problem once the underlying anatomy is understood (Anderson et al, 1987; Figure 11.1). Complete heart block occurred in only three out of 41 patients (7%) in two reported series (Cheung et al, 1990; O'Leary et al, 1992) and this method is still used for many patients at the hospitals in the present study.

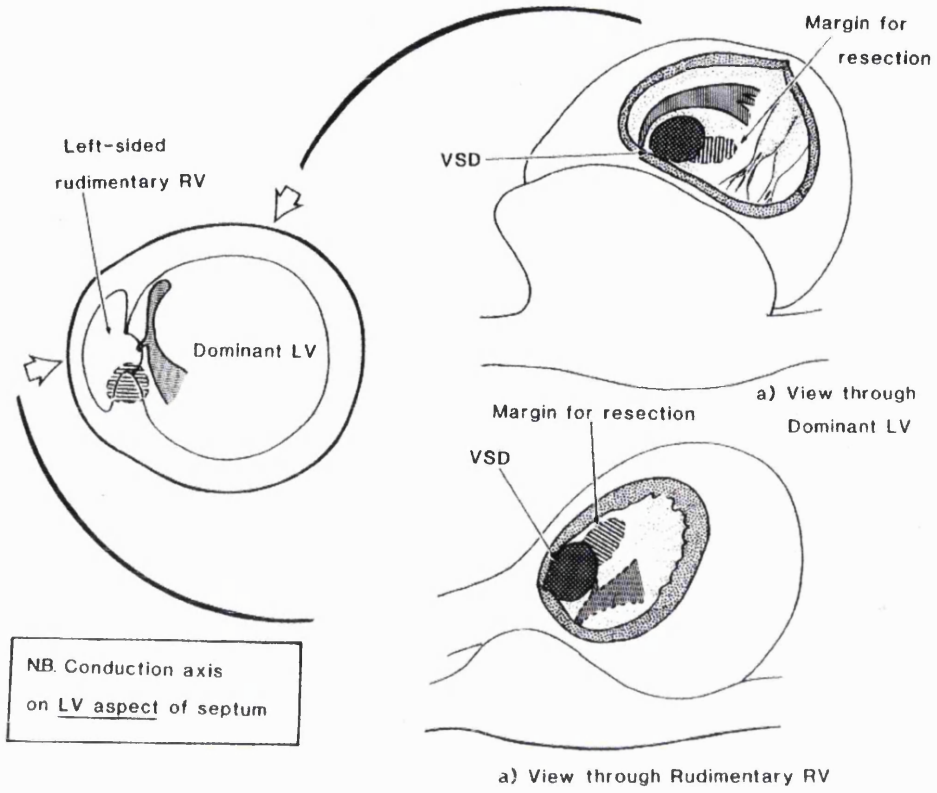

Figure 11.1. Diagram showing the surgeon's view of the conduction tissue in a heart with double inlet left ventricle with a rudimentary anterior left sided right ventricle, discordant ventriculo-arterial connections and subaortic stenosis due to a restrictive ventricular septal defect. The view of the potentially resectable area differs when seen from an approach through the dominant left ventricle compared to the generally preferred right ventricular approach.

LV, left ventricle; RV, right ventricle; VSD, ventricular septal defect.

The current data would support a similarly aggressive strategy for infants without subaortic stenosis at initial presentation, but who have an aortic arch lesion. These patients will inevitably and rapidly develop subaortic stenosis after the conventional palliative approach of banding of the pulmonary trunk together with relief of aortic arch obstruction. This was the outcome irrespective of the relative diameters of the ventricular septal defect and ascending aorta. During the period of the study, the hospitals in the current study tended to undertake a two stage approach by initially

repairing the aortic arch and banding the pulmonary trunk, followed later by either enlargement of the ventricular septal defect (Cheung et al, 1990) or by anastomosis of the ascending aorta to the pulmonary artery with the placement of a systemic-to-pulmonary arterial shunt (Damus-Kaye-Stansel type operation). Currently, this two stage approach is still advocated by these units, as well as others (Jensen et al, 1996), provided that the second stage is undertaken in infancy. This second stage may also be combined with a superior cavopulmonary anastomosis (bidirectional Glenn), as promoted by Webber and colleagues (1992).

In contrast, because of the relatively high risk of these procedures when undertaken in infancy, in patients of less than one year of age without evidence of systemic outflow obstruction at any level, the presenting institutions still advocate the use of isolated banding of the pulmonary trunk. This remains appropriate and effective low risk initial palliation (Stefanelli et al, 1984; Jensen et al, 1996), provided the ventricular septal defect is of adequate size (Franklin et al, 1990; Matitiau et al, 1992). Frequent subsequent investigations by cross sectional and Doppler echocardiography should be undertaken to monitor any tendency to subaortic narrowing and excessive left ventricular hypertrophy.

In older patients, there still remains a higher risk if procedures to relieve subaortic stenosis are combined with definitive surgery (Kirklin et al, 1986; Pacifico, 1986; Caspi et al, 1990). It is therefore strongly advocated by many centres, including the hospitals involved in the present study, that a staged approach be used for most older patients with acquired subaortic stenosis, often combining a bidirectional superior cavopulmonary anastomosis (Glenn) with relief of the subaortic narrowing (Cohen et

al, 1991; O'Leary et al, 1992; Webber et al, 1992; Di Donato et al, 1993; Huddleston et al, 1993; Lui et al, 1993; Brawn et al, 1995; Jensen et al, 1996). In patients in whom there is only mild or trivial restriction to systemic outflow from the left ventricle, surgical relief at the time of definitive surgery is recommended, particularly as subaortic stenosis is still likely to develop due to the natural ongoing process of septal defect closure (Razzouk et al, 1992; Finta et al, 1994).

The question remains as to the influence of initial banding of the pulmonary trunk on the outcome of a subsequent modified Fontan procedure. The Toronto group reported that this procedure was an adverse risk factor to a successful modified Fontan procedure, when undertaken at a mean age of 7.1 years (Coles et al, 1987). This report included patients with concordant ventriculo-arterial connections, who were therefore not at risk of developing subaortic stenosis. Although the same study stated that the operation was associated with the development of subaortic stenosis, no mention was made of the possible influence or presence of aortic arch obstruction. Other investigators have not identified banding of the pulmonary trunk as an incremental risk factor using multivariate analysis (Kirklin et al, 1986; Mayer et al, 1986; Humes et al, 1987; Uemura et al, 1995c). It is clear, however, that increasing age after this palliative intervention does correlate with increasing ventricular hypertrophy (Kirklin et al, 1986; Malcic et al, 1992) and thus a tendency to develop subaortic stenosis. This adds weight to the argument that definitive surgery together with debanding of the pulmonary artery should be undertaken in early childhood for these patients, as discussed in the next Chapter (page 213).

Hearts live by being wounded.

Oscar Wilde (1854 - 1900)

Chapter 12

Implications and future directions

12.1 The use of prediction of outcome methods

This study provides the clinician with a method to predict the likely outcome for a patient presenting to a tertiary institution in the first year of life with any variant of double inlet ventricle or tricuspid atresia in terms of survival, the requirement of palliative surgery and suitability for definitive repair (for tricuspid atresia patients). It has not been tested in a clinical setting but previous work with head injury patients has shown that the use of such predictive methods can positively influence management decisions and interventions in line with 'best practice' without adverse effect (Murray et al, 1993). Currently, doctors are being encouraged to concentrate resources and therapy on patients with the most optimistic outcome who will maximally benefit from their efforts. Although there may be a temptation to limit care and cease active treatment for patients with the worst anticipated outcomes (Knaus et al, 1990), such predictions should be applied with caution. Not only were the present data used as a basis for these assessments retrospectively acquired, but there were also methodological

and statistical limitations, as discussed in Chapter 7 (page 175). Furthermore, the time-scale of the study is historical and does not take into account the most recent surgical and medical advances. Despite these reservations, the method and data provide a unique source of objective information when counselling families and planning future management for an infant with double inlet ventricle or tricuspid atresia, either pre- or postnatally. Nevertheless, such decisions also need to take account of current best practice and the results of therapy at local paediatric cardiology centres. Social, cultural and ethical issues relevant to the individual family also need to be considered in the decision-making process.

12.2 The timing of definitive surgery

Patients with tricuspid atresia and double inlet ventricle, who have survived beyond infancy, are at continued risk of both sudden death and the development of adverse factors to a later successful definitive repair. These include subaortic stenosis, pulmonary arterial distortion and dominant ventricular hypertrophy, fibrosis and dysfunction (Kirklin et al, 1986; Coles et al, 1987; Kuroda et al, 1987; Mietus-Snyder et al, 1987; Moak and Gersony, 1987; Franklin et al, 1990; Mair et al, 1990; Stein et al, 1990; Akagi et al, 1991; Malcic et al, 1992; Allgood et al, 1994; Uemura et al, 1995c; Waldman et al, 1996). Although the question of the optimal age for Fontan-type surgery remains unresolved, the authors in these reports argue in favour of undertaking definitive surgery at a younger age. Of importance and also in support of a policy of 'elective' Fontan-type procedures in younger patients, are several studies which have found that an older age at repair appears to be an adverse factor for long term post-

Fontan survival (Fontan et al, 1990), exercise capacity (Cortes et al, 1994), ventricular contractility (Sluysmans et al, 1992) and the development of late arrhythmias (Gewillig et al, 1992; Cromme-Dijkhuis et al, 1993).

The current data would also support early intervention on several counts. It would potentially reduce the incidence of sudden cardiac death encountered in the present series, by minimising the effects of chronic hypoxia and volume and pressure loads on the myocardium. It is well established that high levels of myocardial fibrosis inhibit diastolic ventricular function (Weber et al, 1993) and this in turn adversely influences survival in the early post-operative period (Gewillig et al, 1990b; Penny et al, 1992). Chronic hypoxia in a canine model has been shown to reduce subendocardial blood flow, leading to a lower threshold for ischaemic injury and secondary fibrosis (Pridjian et al, 1995). In support of these findings are recent histopathological studies that have shown an increase in myocardial collagen content with increasing age, in patients with tricuspid atresia and aortic valve atresia (Ho et al, 1996; Schwartz et al, 1996). Undertaking definitive surgery at an earlier age might reduce such stimuli for the development of myocardial fibrosis and thereby minimise its adverse consequences. In addition, it would alleviate chronic hypoxia induced polycythaemia and microemboli, which can compromise pulmonary function and therefore jeopardise hopes for an eventual successful Fontan-type operation (Olson et al, 1993).

The present study found a high incidence of adverse factors in the patients who had undergone construction of multiple systemic-to-pulmonary arterial shunts during follow-up, particularly in the tricuspid atresia cohort. Earlier timing of definitive repair would obviate the need for a second shunt procedure for most patients who present

initially with reduced pulmonary blood flow. This strategy would avoid the inherent operative risks, the adverse effects of continued volume loading of the functionally single ventricle (LaCorte et al, 1975, Kuroda et al, 1987) and the potential for later pulmonary arterial distortion.

Further support for undertaking definitive surgery at an early age is provided by the finding that cognitive function was inversely related to the age of repair of children with cyanotic congenital heart disease, specifically transposition of the great arteries (Newberger et al, 1984). The age at definitive surgery (a Mustard procedure) ranged from 0.4 to over four years of age and the mean age of assessment was 5.8 ± 0.2 years. However these findings were not confirmed by a more recent study of a similar group of patients, with a median age of repair of 7.5 months and age of assessment of 10.1 years (Oates et al, 1995). Neither of these studies were prospective and importantly, there is no work to date that has assessed cognitive development in patients with chronic hypoxia in whom definitive surgery has (up until relatively recently) been delayed until late childhood or adolescence, as in the present cohort. Nevertheless, there is conclusive evidence that children with cyanotic congenital heart disease have relatively impaired intellectual ability and more behavioural problems at home and at school, when compared to acyanotic children with other forms of heart disease (Linde et al, 1970; Aram et al, 1985; Wray and Yacoub, 1991; Wright and Nolan, 1994). This discrepancy in cognitive functioning between acyanotic and cyanotic children appears to be maintained even after definitive repair. Linde and colleagues' (1970) prospective study found a significant increase in intelligence quotient scores in children with repaired cyanotic heart lesions (excluding tetralogy of Fallot), in comparison to those children with similar but unoperated cyanotic conditions. Unfortunately age at surgery

was not incorporated into their analyses. Below average intellectual functioning may be partly attributable to multiple factors associated within any chronic childhood illnesses, such as under-nourishment, physical incapacity and parental over-protection (Linde et al, 1970; Wray and Yacoub, 1991). These studies lend support to the concept of an earlier age of definitive surgery on the grounds of the intellectual and psychosocial benefits that would result from the early relief of chronic cyanosis.

Physical growth may also be affected by the presence of cyanotic congenital heart disease. Not surprisingly, the excessive energy requirements and expenditure found in children with many forms of congenital heart disease decrease after definitive surgery (Mitchell et al, 1994). Weintraub and colleagues (1991) have proposed that chronic cyanosis and tissue hypoxaemia may primarily inhibit growth by inducing end-organ insensitivity to insulin-type growth factor 1, although a lack of nutritional intake must also play a part in the more seriously unwell child. They also found that growth improved following definitive surgery for cyanotic heart lesions and their data suggest that catch up growth appears not to be so great in those patients operated upon at an older age (Weintraub et al, 1991). This further supports a policy of embarking on definitive surgery once the child has reached an age at which the operative risks are not excessive.

Recent surgical series have not reported an increase in operative mortality after Fontan-type surgery undertaken at a young age (Kirklin et al, 1986; Mayer et al, 1986; Coles et al, 1987), particularly in the current era (Mair et al, 1990; Castaneda, 1992; Pearl et al, 1992; Weber et al, 1992; Kaulitz et al, 1995; Sharma et al, 1995; Uemura et al, 1995c; Cetta et al, 1996). It is unknown however, if early definitive repair will enhance long

term survival and patient functional status. Equally, it is too early to say whether the documented improvements in myocardial indices will be better sustained simply because such surgery was performed during early childhood.

12.3 Intermediate palliation using a bidirectional superior cavopulmonary (Glenn) anastomosis

It is now clear that undertaking additional procedures at the time of a Fontan-type operation, such as reconstruction of distorted pulmonary arteries (Kirklin et al, 1986; Mayer et al, 1986, 1992; Driscoll et al, 1992) or relief of subaortic stenosis (Kirklin et al, 1986; Pacifico, 1986; Caspi et al, 1990), increases operative risks considerably. Furthermore, the presence of significant ventricular hypertrophy is a particularly adverse factor in the early post-operative period (Kirklin et al, 1986; Seliem et al, 1989; Caspi et al, 1990; Fontan et al, 1990; Mair et al, 1990). This is because the separation of systemic and pulmonary venous returns causes the ventricle to contract in size, as its volume load is virtually halved. Previously appropriate muscle hypertrophy to the loading conditions, such as in the presence of a banded pulmonary trunk or the volume load inherent in a systemic-to-pulmonary arterial shunt (LaCorte et al, 1975, Kuroda et al, 1987), then becomes inappropriate. The resultant acute diastolic dysfunction is similar to that found in hypertrophic cardiomyopathy (Gewillig et al, 1990b; Penny et al, 1992) and jeopardises the new Fontan circulation during the critical immediate post-operative period. The trend has therefore been towards the routine use in many institutions of a bidirectional superior cavopulmonary (Glenn) anastomosis (or the similar hemi-Fontan procedure), as an intermediate staging operation between

conventional surgical palliation and definitive surgery, in those who do not fulfil many of the original criteria proposed by Choussat and colleagues in 1978 (Mazzera et al, 1989; Bridges et al, 1990a; O'Leary et al, 1992; Di Donato et al, 1993; Pridjian et al, 1993; Jacobs and Norwood, 1994; Knott-Craig et al, 1995; Vargas et al, 1995). Retrospectively, in the Mayo Clinic experience, this would mean most of their patients would currently require this multistage approach, as 62% of their reported series of 352 patients had two or more such adverse features present (Driscoll et al, 1992). The advantage of this strategy is that by partially unloading the dominant ventricle, the immediate post-surgical changes are less dramatic (Allgood et al, 1994). At the same operative sitting, concurrent adverse features can be dealt with, such as subaortic stenosis (O'Leary et al, 1992; Di Donato et al, 1993) and pulmonary arterial distortion (Pridjian et al, 1993; Mendelsohn et al, 1994). There is then time for regression of unwanted hypertrophy, given the new loading conditions, before completing the separation of pulmonary and systemic venous returns by means of a connecting intracardiac or extracardiac tunnel or conduit between the inferior caval vein and the pulmonary arterial tree.

More acceptable oxygen saturations may be achieved in patients who have undergone a bidirectional superior cavopulmonary anastomosis by leaving a concurrent systemic-to-pulmonary arterial shunt or a pulmonary trunk band intact (Kobayashi et al, 1991; Allgood et al, 1994). This also ensures continued pulsatile pulmonary blood flow and possibly minimises the risks of later developing pulmonary arteriovenous fistulae by allowing the passage of the postulated hepatic factor to the pulmonary vasculature (Srivastava et al, 1995; Webber et al, 1995), as discussed in Chapter 10 (page 192).

The timing of this intermediate stage has come under scrutiny, as has the question of when to complete the total cavopulmonary connection. Given that it would be optimal, as discussed above, to complete this Fontan-type procedure at as early an age as possible, it is encouraging that recent reports have supported the construction of a bidirectional Glenn connection from as young as three months of age (Albanese et al, 1992; Chang et al, 1993; Alejos et al, 1995; Jacobs et al, 1996; Slavik et al, 1996). In fact, a later age at operation may be associated with greater post-operative cyanosis in those over four years of age (Gross et al, 1994). Forbes and colleagues (1996) have also recently reported that those operated upon at over ten years of age appear not to sustain the same benefits as younger patients in terms of significant changes in ventricular volume, mass and functional indices.

Ascertaining the optimal time for surgery to complete the total cavopulmonary connection is complicated by conflicting early reports of follow-up after a bidirectional Glenn procedure or hemi-Fontan operation, often with only small numbers of patients. Two units failed to demonstrate a significant reduction in ventricular mass six to twelve months after the procedure, despite a decrease in ventricular volume (Allgood et al, 1994; Fogel et al, 1996). Another centre reported a diminution of both ventricular mass and volume, but only in those operated on before three years of age (Forbes et al, 1996). Other studies have examined pulmonary arterial growth after these procedures. There is evidence of differential pulmonary arterial growth after as little as 18 months post-surgery (Albanese et al, 1992). However, the maintenance of alternative sources of pulmonary blood flow appears to ameliorate this potential problem and not adversely affect later Fontan-type surgery (Slavik et al, 1995; Uemura et al, 1995d; Reddy et al, 1996). There is also physiological evidence that increasing age with a bidirectional

Glenn circulation will be accompanied by increasing cyanosis (Gross et al, 1994), as the percentage that the superior caval vein blood flow contributes to the total cardiac output falls with normal growth (Salim et al, 1995). Given all of the above concerns, it seems potentially beneficial not to delay the operation to complete the total cavopulmonary connection much more than two or three years after the bidirectional Glenn procedure.

In summary, the optimal timing of staged and definitive surgery has yet to be conclusively delineated, but if adverse factors are present or are likely to develop, then early operative intervention will probably be beneficial. A further dimension is also added by discussions over the place of a fenestrated definitive Fontan-type procedure and its benefits compared to staged surgery, or the use of both techniques (Jonas, 1994). Such matters await the results of further studies and medium term follow-up into the next century.

12.4 Future trends in management

In the 1990s the vast majority of patients (not identified at in utero foetal screening) with either double inlet ventricle or tricuspid atresia will present to tertiary centres in infancy, with or without symptoms. They will then have their lesion virtually completely elucidated by cross sectional echocardiography. Currently, as previously stated, the aim of management at this time is to ensure survival into childhood with suitable anatomy and haemodynamics for later definitive surgery, usually Fontan-type procedure. It is the markedly varied morphological spectrum of the patients in this study, in contrast to other reports, that emphasises and mandates that these management

decisions must be individualised. This process will be facilitated by the use of the unique additive indices with or without the more complex calculations presented here, to derive predicted patient specific survival curves based on the infants' underlying cardiac pathology and physiology. Such decisions also need to take into account continued surgical refinements which may reduce short and long term morbidity and mortality, such as those recently adopted from computer generated flow studies of cavopulmonary anastomoses (de Leval et al, 1996), or others which may minimise the post-operative incidence of arrhythmias (Hashimoto et al, 1995; Gandhi et al, 1996).

Although many future parents will decide against continuing pregnancy when a diagnosis of tricuspid atresia or double inlet ventricle has been made during foetal screening (Allan et al, 1994), contemporary ethical trends seem to be against non-intervention as an option for infants with even the most complex cardiac lesions, once the child is born. For these neonates, the future is likely to be that of multiple staged palliative procedures, particularly for those with multiple associated lesions, even if the ultimate surgical intervention is likely to be cardiac transplantation.

The decision concerning when to intervene in an asymptomatic patient with a good additive score and a high likelihood of definitive surgical success, is more difficult. Evidently, the Fontan operation and its many modifications can best be described as definitive palliative procedures. Increasingly, many patients who have undergone Fontan-type interventions during the 1970s and early 1980s in the early Fontan era are being put on a heart transplant waiting list, although these tend to be patients who originally had borderline pre-operative Fontan criteria. Nevertheless, a plan of management must be made for such relatively well patients, given his or her specific

cardiac malformation. This judgement will need to take into account the risks of early, often staged surgery in individual institutions, along with the largely unknown long term outcome of present day Fontan-type surgery. These factors must then be balanced against the patient's current, often palliated well-being, and probable longer term cardiac and functional deterioration.

In conclusion, the present study provides a comprehensive basis making for such decisions for infants and children with double inlet ventricle or tricuspid atresia, as well as enabling further analyses aimed at improving therapeutic strategies with respect to future surgical and medical innovations.

Appendix A

Risk Factor Analyses

The morphological and physiological variables (or 'factors'), as assessed at initial presentation to the tertiary centres and listed in Table 4-3 (page 89) for patients with double inlet ventricle and Table 5-3 (page 133) for patients with tricuspid atresia, were used for the various risk factor analyses. Each variable consisted of a list of possible categories and a particular category was then selected to act as a *baseline category* for later analysis. This usually was the most common category numerically and thus corresponded to the most 'normal' category with respect to the 'average' patient with either double inlet ventricle or tricuspid atresia. The relative risk (i.e., the proportional increase in hazard) associated with each non-baseline category, within each variable was measured with respect to this baseline category. The baseline category had a relative risk of 1.00. The important assumption was made that such relative risks would remain fixed until the time of definitive surgery or the date when last seen (the "proportional hazards assumption"; Cox and Oakes, 1985).

Firstly, a univariate analysis was used to examine each variable independently and relative risks were calculated for the different categories within each variable, with respect to the relevant baseline category within that variable. The results are listed in Tables 4.3 and 5.3.

Multivariate analysis was then performed using all the variables simultaneously to estimate relative risks in a Cox model of proportional hazards (Cox and Oakes, 1985). These results are also listed in Tables 4-3 and 5-3. The calculation required that each distinct category was given a unique label **i** with the relative risk associated with that category being represented as $\mathbf{r_i}$. Thus, for the baseline categories $\mathbf{r_i = 1.00}$. The Cox proportional model then assumed that at any point in time before definitive surgery, a patient with presenting features with labels in a set **I** had a relative risk of dying of **RR** (relative to the 'baseline' patient who, by definition had all the baseline categories), as given by:

$$\mathbf{RR = product \{ r_i ; i \text{ in } I \}}$$

This provided a means to estimate the outcome of an individual infant when first assessed at a tertiary centre with any morphological or physiological variant of double inlet ventricle or tricuspid atresia. A calculated total relative risk was produced for such a patient by multiplying together all of the resulting multivariate relative risks. No selection of factors on the basis of statistical significance was made, as this would inappropriately equate 'not statistically significant' with 'equal to zero'. This total relative risk was then used to adjust the estimated survival of the notional 'baseline' patient, who had a total relative risk of 1.00. Hence, a predicted survival curve for an individual patient with a particular combination of risk factors could then be estimated, by taking the survival probabilities of this 'baseline' patient at different ages (Tables A-1 and A-2), to the power of the total relative risk of that patient (Kalbfleisch and Prentice, 1980). To illustrate this method, examples are detailed below for a patient

with double inlet ventricle and one with tricuspid atresia, which correspond to the two cases described in the legends below Tables 4-3 and 5-3.

i) The notional 'baseline' patient for the patients with double inlet ventricle had the following categories present: usual atrial arrangement, double inlet left ventricle via two atrioventricular valves, discordant ventriculo-arterial connections and normal pulmonary venous connections, without systemic or pulmonary outflow tract obstruction. The patient presented with high pulmonary blood flow, without significant acidosis, at less than two weeks of age, after 1979. To estimate the survival at one year of the patient described in the text on page 91, with a total relative risk of 0.096, the survival of the 'baseline' patient at one year, estimated to be 0.644 (Table A-1), is taken to the power of 0.096. This gives a predicted survival at one year of 0.959 or 96%. Similarly at five years, the predicted survival would be 0.328 to the power of 0.096, which equals 0.898 or 90%, as plotted in Figure 4.4 - curve A. Using this method a series of estimated survival curves were produced for patients with other common variants of double inlet ventricle (Figures 4.4 and 4.5, pages 92, 93).

ii) For tricuspid atresia patients, the notional 'baseline' patient was defined as having the following categories present: concordant ventriculo-arterial connections, a non-restrictive atrial communication and no systemic or pulmonary outflow tract obstruction. The patient presented with low pulmonary blood flow, without significant acidosis, at less than two weeks of age, after 1979. Thus, a predicted survival curve for a patient with a particular combination of the factors in Table 5-3 was estimated by taking the survival probabilities of the 'baseline' patient at different ages (Table A-2) to the power of the total relative risk of that patient. Using the example from the text on

page 135, with a total relative risk of 0.126, the predicted survival at one year would use the survival of the 'baseline' patient at one year, estimated to be 0.773, to the power of 0.126, giving a predicted survival at one year of 0.968 or 97%. At five years the predicted survival would be 0.589 to the power of 0.126, which equals 0.935 or 93%, as plotted in Figure 5.3, curve A. A series of estimated survival curves for patients with other variants of tricuspid atresia was also produced (Figures 5.3 and 5.4, pages 136, 137).

A simpler method of stratifying neonates into risk groups was then created by exploiting the fact that:

$$\log (RR) = \text{sum} \{ \log (r_i) ; i \text{ in } I \}$$

The natural logarithm of each of the estimated relative risks, as given by $\log (r_i)$, was then simply rounded to the nearest integer to produce an additive index, as detailed in Tables 4-4 and 5-4 (pages 95 and 138).

Table A-1. Estimated probability of survival for the 'baseline' patient with double inlet ventricle

Duration of survival after presentation (months)*	Estimated survival (proportion)
0.25	0.975
1	0.874
3	0.783
6	0.719
12	0.644
24	0.530
36	0.489
48	0.404
60	0.398
120	0.389

* Time zero is the date of first presentation to the tertiary centre.

Table A-2. Estimated probability of survival for the 'baseline' patient with tricuspid atresia

Duration of survival after presentation (months)*	Estimated survival (proportion)
0.25	0.974
1	0.937
3	0.883
6	0.822
12	0.773
24	0.673
36	0.618
48	0.593
60	0.589
120	0.528

* Time zero is the date of first presentation to the tertiary centre.

Appendix B

Analysis of the effects of palliative surgery

This analysis was limited to the patients with double inlet ventricle. Palliative surgery was undertaken on 152 occasions for 121 of these patients, as detailed in Table 4-6 (page 98). The post-operative hazard rates (instantaneous monthly risk of death) prior to definitive surgery for the three main palliative procedures are given in Table B-1, and correspond to Figure 4.8 (page 101). The effects of this surgery were assessed by means of a proportional hazards analysis, with added time-dependent covariates indicating various periods of time following palliative surgery. These additional risk factors were 'turned on' and 'turned off' again, within particular time periods. The overall severity of the palliated heart lesion was assessed by taking into account the variables listed in Table 4-3 (page 89) as calculated in the multivariate, multiplicative analysis. The coefficients were now newly estimated to incorporate simultaneously the effects of the operations (Table B-2). This process was undertaken for palliative surgery overall and for each of the three main palliative procedures: the construction of a systemic-to-pulmonary arterial shunt, isolated banding of the pulmonary trunk and banding of the pulmonary trunk together with relief of aortic arch obstruction. This technique allowed patients of a similar age and with similar morphological characteristics (i.e., a near matched underlying total relative risk), but who had not received the corresponding operation, to be used as matched 'controls'.

Thus, consider a patient with baseline features with labels in **I**, who had a palliative operation at time **d**. Then, the relative risk at time **t** before definitive surgery, **RR (t)**, (relative to a patient with all the baseline categories, who had not undergone palliative or definitive surgery) is given by the following equation:

$$\mathbf{RR\ (t)\ =\ product\ \{\ r_i\ ;\ i\ in\ I\ \}\ .\ r_p(t)\ .\ R_S(t)\ .\ r_m(t)}$$

where:

$$\mathbf{r_p\ (t)\ =\ r_p\ if\ d < t < d + 1\ month}$$

$$\mathbf{=\ 1\ otherwise;}$$ (post-operative relative risk)

$$\mathbf{r_s\ (t)\ =\ r_s\ if\ d + 1\ month < t < d + 6\ months}$$

$$\mathbf{=\ 1\ otherwise;}$$ (short term relative risk)

$$\mathbf{r_m\ (t)\ =\ r_m\ if\ d + 6\ months < t}$$

$$\mathbf{=\ 1\ otherwise.}$$ (medium term relative risk)

Table B-1. Post-operative hazard rates (instantaneous monthly risk of death) prior to definitive surgery, for the 110 patients with double inlet ventricle who underwent the three main palliative procedures

Months	Systemic-to-pulmonary arterial shunt	Banding of the pulmonary trunk	Banding of PT with aortic arch repair
0 - 1	0.152	0.123	0.667
1 - 3	0.032	0.035	0.063
3 - 6	0.015	0.025	0.000
6 - 12	0.004	0.000	0.000
12 - 24	0.002	0.007	0.028
24 - 60	0.006	0.005	0.009
60 - 120	0.002	0.000	0.000

PT, pulmonary trunk.

Table B-2. Multivariate risk factor analysis for the 191 patients with double inlet ventricle using factors as found at initial presentation: with and without the incorporation of the risk factors for palliative surgery - I

Variable and categories	N	%	Relative risk: without (95% CL)		Relative risk: with (95% CL)	
Atrial arrangement (situs)						
Usual (solitus) †	137	72		**p = 0.02**		**p = 0.02**
Mirror-image (inversus)	6	3	0.47	(0.14, 1.60)	0.50	(0.14, 1.76)
Right isomerism	34	18	1.45	(0.71, 2.95)	1.56	(0.74, 3.27)
Left isomerism	14	7	0.38	(0.14, 1.01)	0.41	(0.15, 1.10)
Dominant ventricular morphology						
Left †	136	71		**p = 0.13**		p = 0.14
Right	34	18	0.54	(0.29, 0.99)	0.49	(0.27, 0.90)
Indeterminate	21	11	0.81	(0.38, 1.71)	0.84	(0.39, 1.79)
Mode of atrioventricular connection						
Two atrioventricular valves †	110	58		**p = 0.30**		**p = 0.30**
Common atrioventricular orifice	81	42	1.35	(0.77, 2.37)	1.34	(0.74, 2.41)
Ventriculo-arterial connections						
Discordant †	85	44		**p = 0.01**		**p = 0.01**
Concordant	17	9	1.85	(0.89, 3.87)	1.75	(0.81, 3.76)
Pulmonary atresia ‡	38	20	1.93	(0.57, 6.51)	2.32	(0.65, 8.28)
Aortic atresia / truncus	4	2	4.73	(1.16,19.28)	6.23	(1.35,28.75)
Double outlet ‡	47	25	3.40	(1.64, 7.06)	3.17	(1.53, 6.52)
Pulmonary valvar and/or subvalvar obstruction						
Absent †	115	60		**p = 0.03**		**p = 0.04**
Present	76	40	0.35	(0.13, 0.92)	0.50	(0.17, 1.43)
Systemic outflow obstruction						
Absent †	157	82		**p = 0.01**		**p = 0.01**
Present	34	18	2.33	(1.25, 4.32)	2.47	(1.03, 6.00)

Table B-2. Multivariate risk factor analysis for the 191 patients with double inlet ventricle, using factors as found at initial presentation: with and without the incorporation of the risk factors for palliative surgery - I I

Variable and categories	N	%	Relative risk: without (95% CL)		Relative risk: with (95% CL)	
Anomalous pulmonary venous connections						
Absent (normal) †	163	85		**p < 0.0001**		**p < 0.0001**
Present	28	15	4.83	(2.41, 9.72)	5.17	(2.55,10.44)
Pulmonary blood flow at presentation						
High †	86	45		**p = 0.23**		**p = 0.24**
Low	87	46	1.28	(0.46, 3.56)	1.99	(0.66, 5.97)
Balanced	18	9	0.51	(0.15, 1.65)	0.59	(0.17, 1.98)
Severe acidosis at presentation						
No acidosis †	168	88		**p < 0.0001**		**p < 0.0001**
Acidosis present	23	12	16.56	(7.36,37.32)	28.21	(11.23,70.89)
Age at initial presentation						
Less than 2 weeks of age †	129	67		**p < 0.003**		**p < 0.003**
Two weeks - 2 months of age	36	19	0.54	(0.29, 1.00)	0.46	(0.25, 0.94)
After 2 months of age	26	14	0.23	(0.09, 0.60)	0.22	(0.08, 0.58)
Era of initial presentation						
After 1979 †	77	40		**p = 0.001**		**p < 0.001**
Prior to 1980	114	60	2.16	(1.36, 3.42)	2.30	(1.43, 3.67)

† Baseline category ‡ Both ventriculo-arterial outlets may arise from either the dominant or rudimentary ventricle. CL, confidence limits.

To calculate the total relative risk of a patient with a particular variant of double inlet ventricle at initial presentation, all of the relative risks for that patient are multiplied together, as described in Chapter 4 (page 91).

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