# Pediatric Cardiology

# Pediatric Cardiology:

## *How It Has Evolved over the Last 50 Years*

By
P. Syamasundar Rao

Cambridge
Scholars
Publishing

Pediatric Cardiology: How It Has Evolved over the Last 50 Years

By P. Syamasundar Rao

This book first published 2020

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library



ISBN (10): 1-5275-4888-0
ISBN (13): 978-1-5275-4888-6

**This book is dedicated to:**

*My parents*

***Late Sri PVB Krishna Rao, Late Srimathi Patnana Savithramma***

*My grandparents*

***Late Sri Patnana Swamy Chetty and Late Srimathi Patnana Rathnalamma***

*My teachers*

***Dr Lavanya Muhkerjee, Dr Herman W Lipow, Dr Norman J Sissman***

***Dr Jerome Liebman, Dr Leonard M Linde***

*My wife and children*

***Mrs Hymavathi Rao Patnana, Dr Vijay Kumar Patnana, Dr Madhavi Patnana, and Miss Radhika Patnana***

# CONTENTS

# PREFACE

The field of pediatric cardiology was in its early development when I began my career in the mid-1960s. I had the opportunity to witness first-hand the stepwise evolution of pediatric cardiology over the last 50 years. Therefore, I can provide a unique historical perspective. I have given considerable attention to the development of new knowledge while providing care to patients with heart disease over a 50-year period. This book describes these developments, along with my contributions to pediatric cardiology. This book is being published concurrently with my memoir, which portrays my life journey, and serves as a companion to it. The main purpose of this book is to bring together the advances in pediatric cardiology, particularly the management of congenital heart defects. Along the way, the art and science of interventional pediatric cardiology will be presented, as applicable to each chapter.

Developments such as the early detection of neonates with serious heart disease and their rapid transport to tertiary care centers, the availability of highly sensitive noninvasive diagnostic tools, advances in neonatal care and anesthesia, progress in trans-catheter interventional procedures and the extension of complicated surgical procedures to the neonate and infant have advanced to such a degree that almost all congenital cardiac defects can be diagnosed and "corrected". The defects that cannot be corrected can be effectively palliated. Cardiac defects that were once fatal in infancy are now treatable. These principles will be incorporated into the respective chapters, as applicable. Although every attempt was made to minimize repetition, there was some degree of replication which was unavoidable in order to preserve continuity of thought/discussion.

**P. Syamasundar Rao, MD**

# ACKNOWLEDGEMENTS

Apart from those mentioned in the dedication, I wish to acknowledge the patients and their parents who kindheartedly participated as volunteer research subjects in the numerous clinical trials quoted in this book, and thank them for their courage and wisdom. An equal credit goes to the physicians, nurses and cardiologists of these subjects who convinced their patients and the parents of children to participate in these clinical studies. These individuals, through their kind efforts, advanced/created a knowledge base which is likely to form a foundation of immense implication for generations of patients in the future.

During a multitude of academic endeavors over the last 50 years, I collaborated with a number of my teachers and colleagues, post-doctoral fellows, resident physicians, medical students, nurses/nurse practitioners, electrocardiography, echocardiography and cardiac catheterization technologists, and statisticians; these are too numerous to list, but are included in the references throughout the book. While the contributions of these individuals were partly acknowledged at the times of their respective publications by their inclusion in the list of authors, it is prudent to thank them again in this book for their contribution, counsel and cooperation.

Finally, I thank Dr. William B. Strong, my senior associate when I was at the Medical College of Georgia, for his continued support even after I left the institution by the way of continued encouragement of my professional and academic activities.

**P. Syamasundar Rao, MD**

# CHAPTER 1

# THE AUTHOR'S JOURNEY

## Introduction

The field of pediatric cardiology was in early development when the author began his career in the mid-1960s. He has had the opportunity to witness the stepwise evolution of pediatric cardiology over the last 50 years. This book describes these developments, along with the author's contributions to pediatric cardiology. The purpose of this book is to comprehensively document the advances in pediatric cardiology, particularly those made in the management of congenital heart defects. Along the way, the art and science of interventional pediatric cardiology will be reviewed, as applicable to each chapter. This chapter introduces the author's journey.

## The Journey

While the author was a student at Andhra Medical College, Visakhapatnam (one of the ten medical schools in India at the time of independence), he was considering the career choices of either becoming a surgeon or a pediatrician. Suddenly, during the house-surgeoncy, the author was faced with taking care of two blue (cyanotic) babies to whom only blow-by oxygen could be given; unfortunately, both babies died. These babies turned out to have severe congenital heart defects, namely, the transposition of the great arteries and tricuspid atresia, respectively. This prompted the thought that the author should go to the USA, train to become a pediatric cardiologist, and return to India to serve the people. This thought would probably have dwindled away, but for the fact that one of the author's professors, Dr. Laxhmana Rao, who had just returned from the USA following a sabbatical at Johns Hopkins University, Baltimore, Maryland, invited Dr. Helen B. Taussig (who is considered to be the mother of pediatric cardiology) to visit the author's medical school. The faculty and staff of the Department of Pediatrics presented a series of patients with heart disease to Dr. Taussig during a three-day period. Dr. Taussig reviewed the clinical, chest x-ray, electrocardiographic (ECG) and blood work findings of these children and discussed each case in a great detail. The author was fortunate to attend these discussions which further strengthened his desire to become a pediatric cardiologist. Less than two years later, he ended up in the USA, completed general pediatric training and attempted to go to Johns Hopkins University Hospital for pediatric cardiology training. Unfortunately, this was not possible because the fellowship funding at Johns Hopkins at that time required immigrant or citizenship status (the author was on a J-1 visa). Fortunately, he was able to secure training at Stanford University, Palo Alto, California, Case-Western Reserve University, Cleveland, Ohio, and the University of California at Los Angeles, California.

His attempts to return to India immediately after training were unsuccessful[1] and this resulted in him accepting a faculty position (Assistant Professor) in 1972 at the Medical College of Georgia in Augusta, Georgia. By 1979, the author had risen to the rank of full Professor. Subsequently he served as Consultant Pediatric Cardiologist and Chairman of Pediatrics at the King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; Professor & Director of Pediatric Cardiology at the University of Wisconsin Medical School, Madison, Wisconsin, as well as the St Louis University School of Medicine, St. Louis, Missouri, and the University of Texas McGovern Medical School, Houston, Texas, in that order. During this period of nearly 50 years of pediatric cardiology practice, the author has, in addition to taking care of patients with heart disease, paid considerable attention to the development of new knowledge, and trained and taught physicians around the world. His interest in clinical research resulted in the publication of more than 390 papers in journals (as first or senior author), 230 abstract presentations, 14 monographs and books, and 150 book chapters, as well as 160 invited presentations and lectureships. For further details of the author's journey, the reader is referred to chapters one through four of his memoir,[2] which is being published concurrently with this book.

## Clinical Research Endeavors

The results of the author's clinical research endeavors as they relate to the evolution of pediatric cardiology over the last 50 years will be reviewed under the following categories in the ensuing chapters: 1. Physiologically advantageous ventricular septal defects; 2. Tricuspid atresia; 3. Electrocardiography; 4. Echocardiography; 5. Cardiac catheterization and cine-angiography; 6. Trans-catheter interventions; and 7. Miscellaneous.

## References

1. Rao PS. The Journey of an Indian Pediatric Cardiologist Dr. K. C. Chaudhuri Lifetime Achievement Award/Oration at AIIMS, New Delhi, September 2017. Indian J Pediat 2017; 84:848-58.
2. Rao PS. The journey of an Indian-American pediatric cardiologist, a memoir, with emphasis on scientific contributions to the medical literature. BookBaby, Pennsauken, NJ., 2020

# CHAPTER 2

# STATISTICS

## Introduction

The author has been involved in a number of clinical studies over the years, and knowledge of statistics is of great importance in the conduct of these studies. Since his education in statistics was minimal during medical school and his residency training in pediatrics, the author took a statistics course at Stanford University during the first year of his pediatric cardiology fellowship, which was helpful. The author has also organized lectures by the Department of Statistics for the pediatric cardiology fellows while at the Medical College of Georgia; the attendance of these lectures re-affirmed the author's understanding of statistical concepts. In addition, the assistance of several statistics books was sought time to time again to expand the author's statistical horizon. Furthermore, a number of statisticians – Robert J. Haggard and Rollie J. Harp of the Medical College of Georgia, Patrick Carey, Rebecca Langhough, and Rebecca Koscik of University of Wisconsin, and Brain Waterman and James W. Hormann of St. Louis University – have helped the author in the statistical analysis and interpretation of the data in several clinical investigations.

## Statistical Analysis

Initially the data were examined to see if they were normally distributed (Gaussian distribution); this was usually performed using the Kolmogorov-Smirnov method or similar tests. Data were expressed as mean ± standard deviation (SD) or standard error of mean (SEM) for continuous, normally distributed variables. Medians and ranges were given when the data were not normally distributed (i.e., data with skewed distribution). Values before and after an intervention (for example, catheter interventions before and after balloon dilatation, or between the pre-occlusion and post-occlusion of cardiac defects) were compared by two-tailed or paired *t* tests. Independent sample *t* tests (analysis of variance) were used for between-group comparisons of normally distributed variables. Fisher's exact, Kruskal-Wallis, McNemars, or Mann-Whitney tests or other chi-squared tests were used, as appropriate, for between-group comparisons of categorical, ordinal, or not normally distributed variables. The level of statistical significance was set at $p < 0.05$. When multiple comparisons were made, the Bonferroni correction was applied.[1]

## Other Types of Statistical Analysis for Special Circumstances

### Multivariate Logistic Regression

Multivariate logistic regression analysis was performed to identify predictors of restenosis following balloon dilatation for stenotic lesions such as pulmonary stenosis, aortic stenosis and coarctation of the aorta.[2-6]

### Actuarial Analysis of Event Free Rates

The actuarial analysis of event-free rates was calculated using the Kaplan-Meir method.[7] This analysis was used to determine event-free rates following balloon pulmonary valvuloplasty (Figure 1-1),[8] balloon angioplasty of aortic coarctation (Figure 1-2),[9] balloon aortic valvuloplasty (Figure 1-3),[10] trans-catheter occlusion of atrial septal defects (ASDs) (Figures 1-4 & 1-5)[11-13] and patent ductus arteriosus (PDA) (Figure 1-6).[14] Similar actuarial analysis was performed to evaluate of rates of resolution of residual shunts following the closure of ASDs[11-13] and PDAs.[14-16]

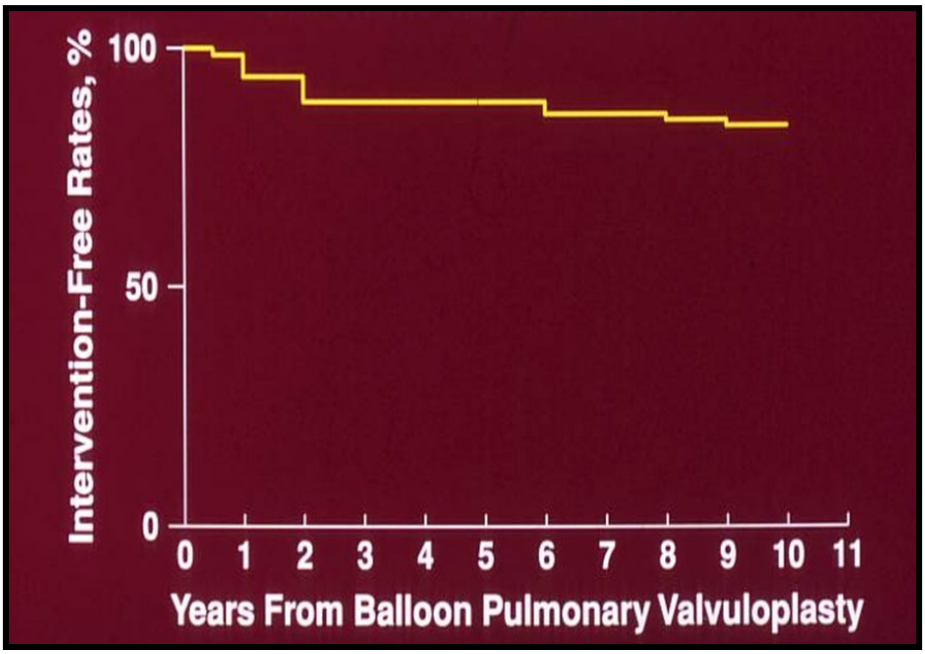


**Figure 2-1.** Actuarial event-free rates after balloon pulmonary valvuloplasty. Re-intervention-free rates at one, two, five, and 10 years after the procedure are 94%, 89%, 88%, and 84%, respectively. Reproduced from Rao PS, et al., Heart 1998; 80:591-5.

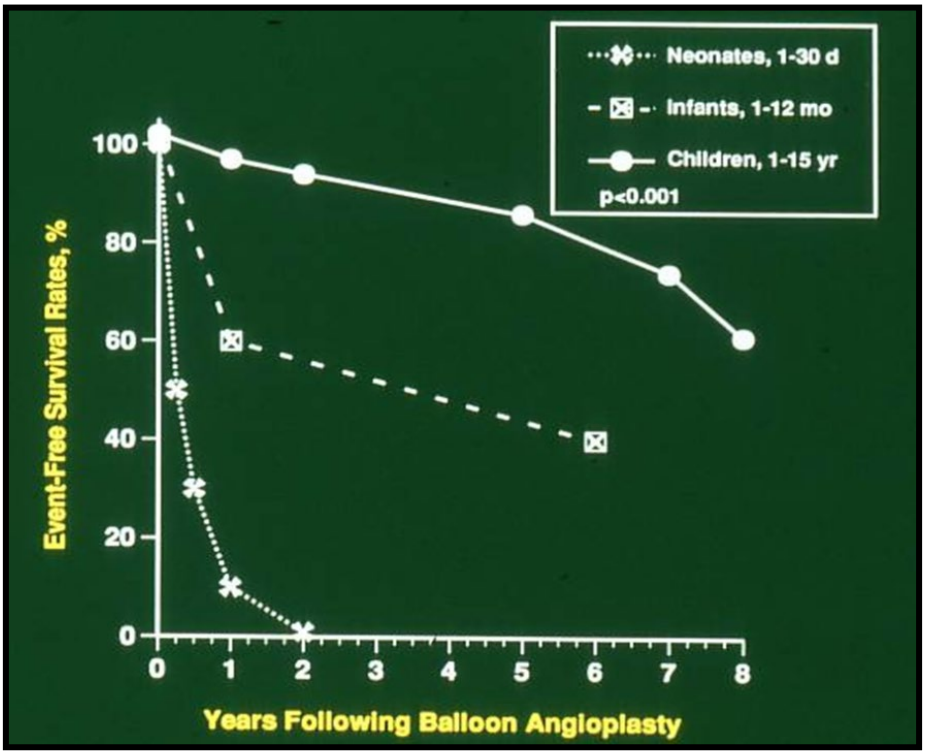


**Figure 2-2**. Actuarial event-free survival curves of neonates (< 30 days), infants (1 to 12 months) and children (1 to 15 years) who had undergone balloon angioplasty of aortic coarctation. The event-free survival rates are better for the children than for the neonatal and infant groups ($p < 0.001$). Reproduced from Rao PS, et al., J Am Coll Cardiol 1996; 27:462-70.

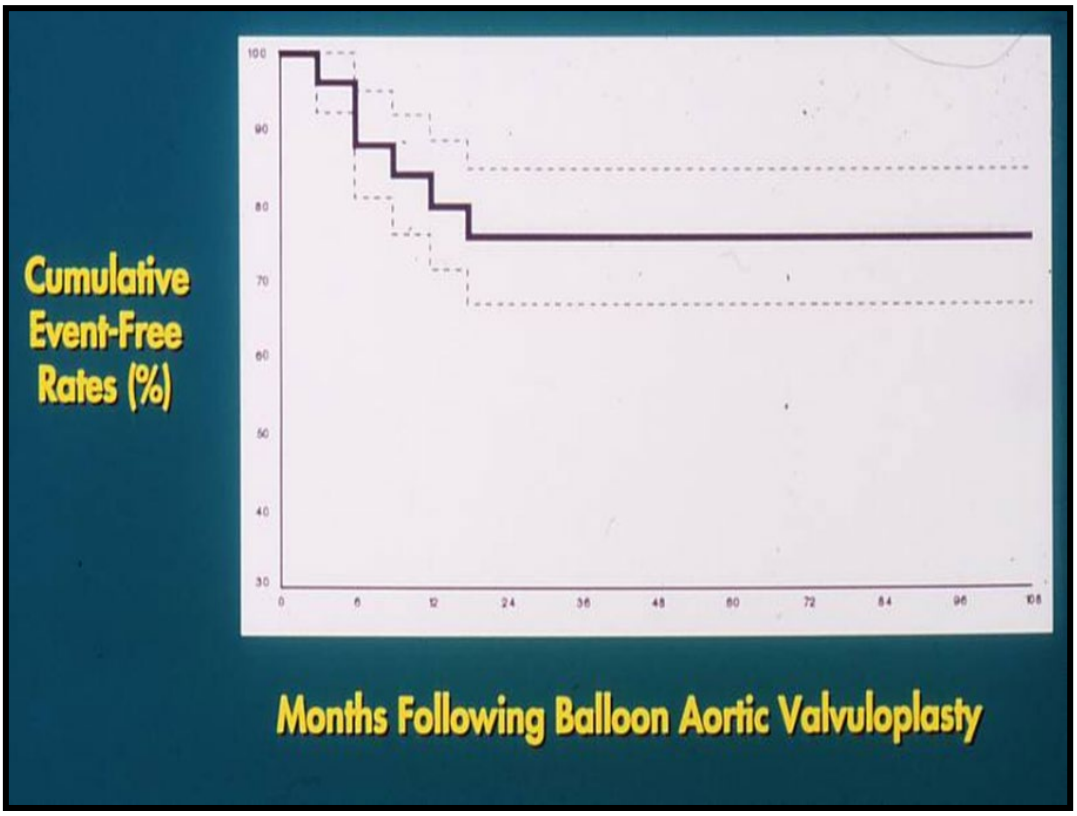


**Figure 2-3.** Actuarial event-free rates after balloon aortic valvuloplasty. 70% confidence limits are marked with dashed lines. Note intervention-free rates at 1, 2, 5, and 9 years are 80%, 76%, 76%, and 76%, respectively. Modified from Galal O, Rao PS, Al-Fadley F, et al., Am Heart J 1997; 133:418-27.

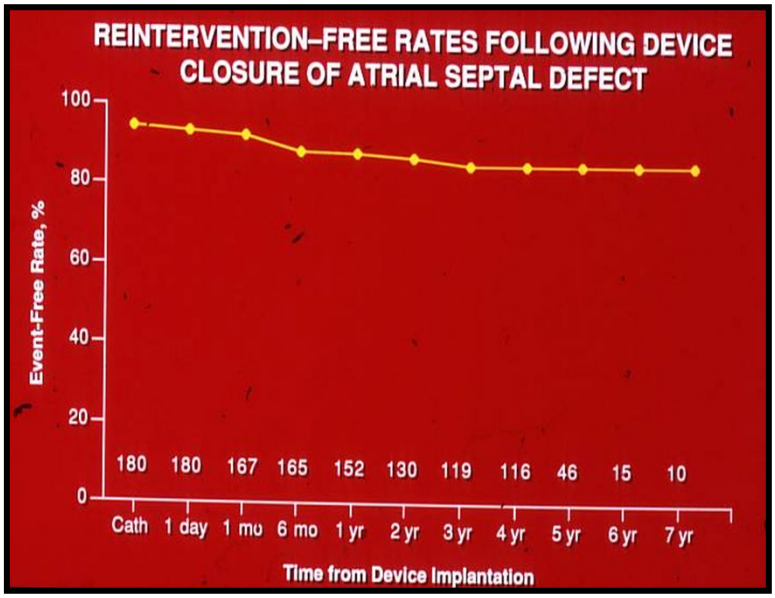


**Figure 2-4.** Graph depicting actuarial event-free rates following trans-catheter buttoned device occlusion of atrial septal defects. Note high (85%) event-free rates at 7 years following device implantation. Modified from Rao PS, Sideris EB. J Intervent Cardiol 1998; 11:467-84.

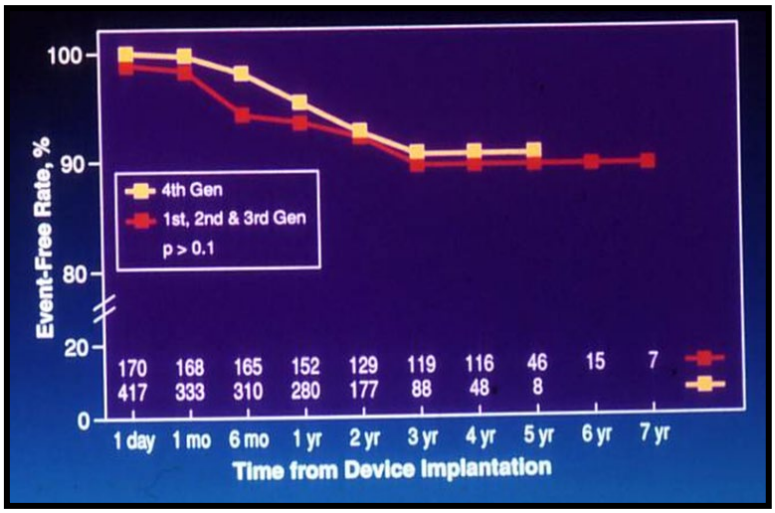


**Figure 2-5.** Graph comparing event-free rates after successful device implantation of first, second and third generation vs. fourth generation buttoned device to close secundum atrial septal defects. The fourth generation (Gen) data are depicted by filled yellow squares and the first, second and third generation by filled red squares. The number of patients available for follow-up at each specified follow-up interval is shown at the bottom of the graph. No difference ($p > 0.1$) by log-rank test was seen between the two cohorts. Modified from Rao PS, et al., J Am Coll Cardiol 2000; 36:583-92.

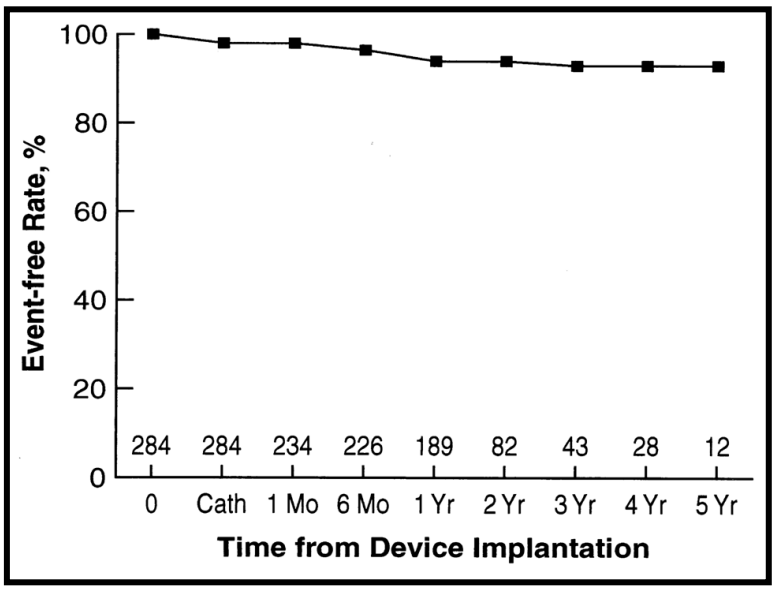


**Figure 2-6.** Graph showing actuarial event-free rates after transvenous buttoned device occlusion of patent ductus arteriosus. Reproduced from Rao PS, et al., J Am Coll Cardiol 1999; 33:820-6.

## Actuarial Analysis of Event Free Rates Using the Grunkemeier and Starr Method

A slightly different method of actuarial analysis (the method of Grunkemeier and Starr[17,18]) was used for expressing patient survival and complication-free survival rates (Figure 2-7) as well as valve survival rates (Figures 2-8 & 2-9) following prosthetic valve replacements in children.[18-20] The survival curves were compared using log-rank tests.[19-21] Thromboembolic and bleeding complications during anti-coagulant therapy following prosthetic valve replacements in children were expressed as linearized rates, i.e., the number of events per 100 patient-years, expressed as a percentage.[19]

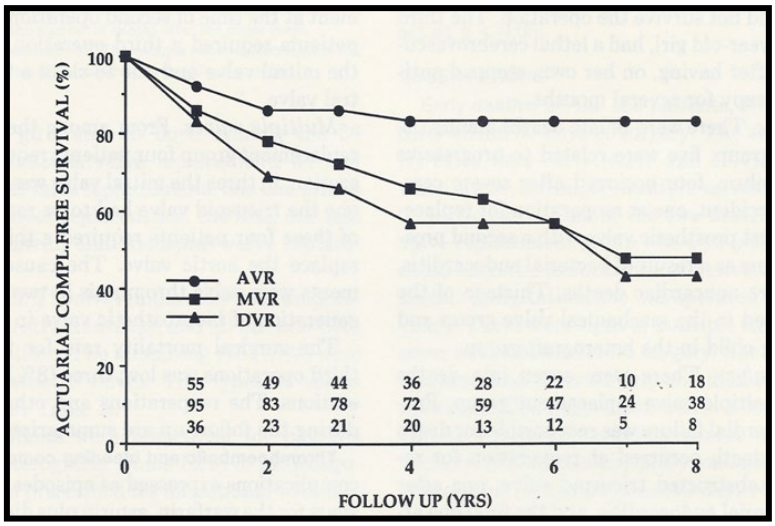


**Figure 2-7.** Actuarial major complication-free survival curves for aortic (AVR), mitral (MVR), and double (DVR) valve replacement are shown. Complication-free survival rates are better for AVR than for MVR and DVR. Similar complication-free survival rates for MVR and DVR suggest that mitral prostheses are largely responsible for complications. Reproduced from Solymar L, Rao PS, et al., Am Heart J 1991; 121:557-68.

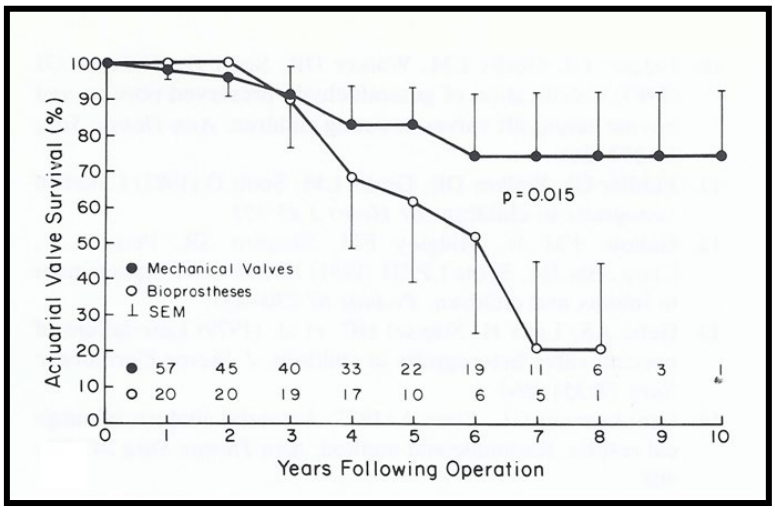


**Figure 2-8.** Actuarial valve survival curves for children ≤ 15 years are shown for mechanical (closed circles) and porcine heterografts (open circles); note the poor survival rate for heterografts (p = 0.015). The confidence limits are marked on only one side of the curve to clearly differentiate both curves. Reproduced from Rao PS, et al., Pediat Cardiol 1991; 12:164-69.

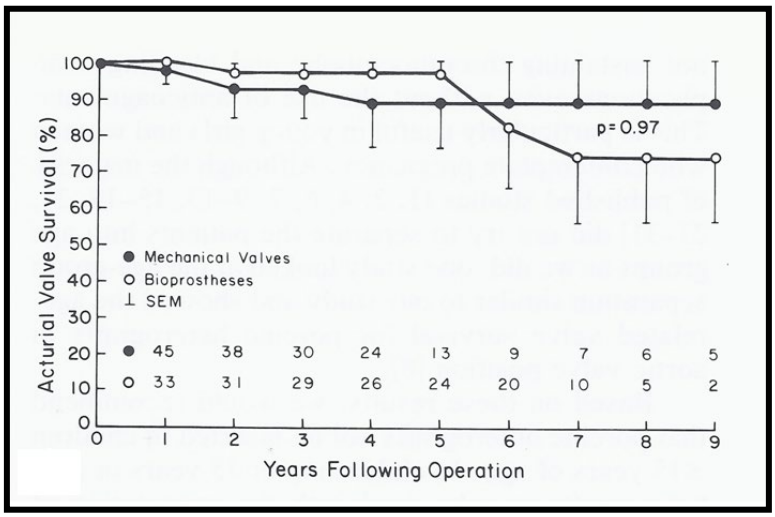


**Figure 2-9.** Actuarial valve survival curves for children > 15 years are shown for mechanical and porcine heterografts; the survival curves are similar (p = 0.97). The confidence limits are marked on only one side of the curve in order to visualize both curves clearly. Reproduced from Rao PS, et al., Pediat Cardiol 1991; 12:164-69.

## Linear Regression and Correlation Coefficients

Linear regression analysis was performed by comparing measured and calculated variables, and between different types of variables, depending on the type of study. Correlation coefficients were calculated to determine the statistical relationship between two variables; Spearman's correlation coefficient (R) was most often used. Values closer to +1 or -1 were considered significant. An example is shown in figure 2-10 in which left ventricular muscle mass was plotted against hemoglobin values with an R value of 0.74 and with a $p < 0.001$.[22] Other examples of correlations of Doppler and echo variables are shown in figures 2-11 through 2-15.[23-25]

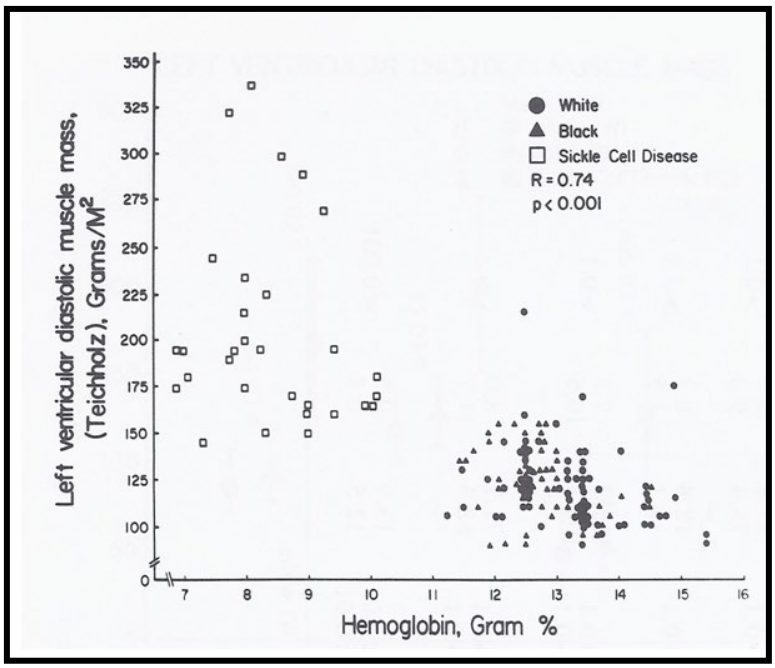


**Figure 2-10.** Left ventricular muscle mass in diastole, calculated using the Teichholz method, is plotted against hemoglobin. Note the significant ($R = 0.74$; $p < 0.001$) correlation between these parameters. Similar correlations were noted between the diastolic and systolic left ventricular muscle mass, calculated by all three methods on the one hand, and hemoglobin values on the other. Reproduced from Rao PS, et al., J Cardiovasc Ultrasonography 1983; 2:381-9.

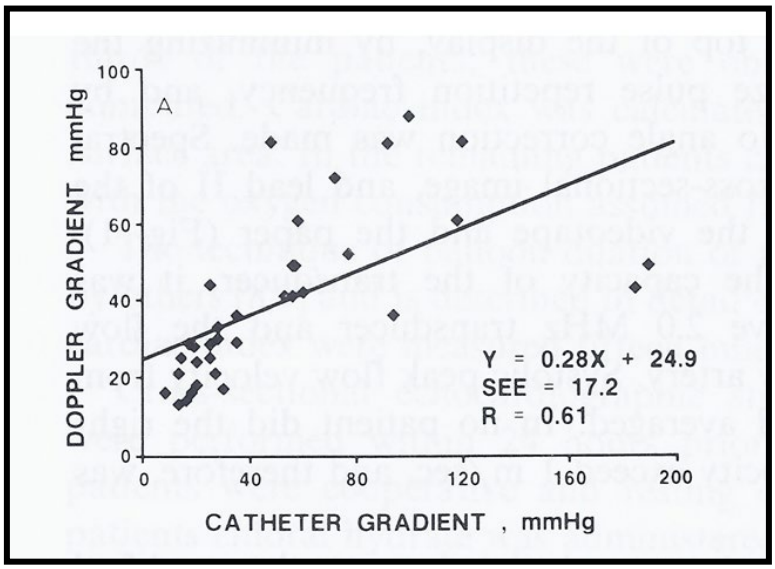


**Figure 2-11.** A scattergram demonstrating the relationship of Doppler-derived (by modified Bernoulli equation) peak instantaneous and catheterization-measured peak-to-peak pulmonary valve systolic pressure gradients is shown. Note that the linear regression analysis indicated a correlation coefficient (R) of 0.61. Reproduced from Rao PS., International J Cardiol 1987; 15:195-203.

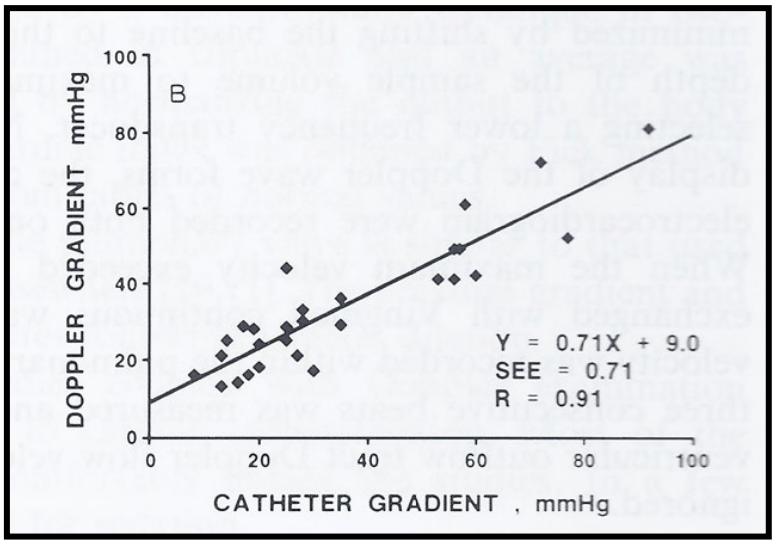


**Figure 2-12.** A scattergram demonstrating the relationship of Doppler-derived (by modified Bernoulli equation) peak instantaneous and catheterization-measured peak-to-peak pulmonary valve systolic pressure gradients is shown; this is similar to Figure 2-11, but after the removal of data sets from five patients with severe stenosis and one patient with severe infundibular stenosis. Note that the linear regression analysis indicated improvement in the correlation coefficient (R) to 0.91. Reproduced from Rao PS, International J Cardiol 1987; 15:195-203.

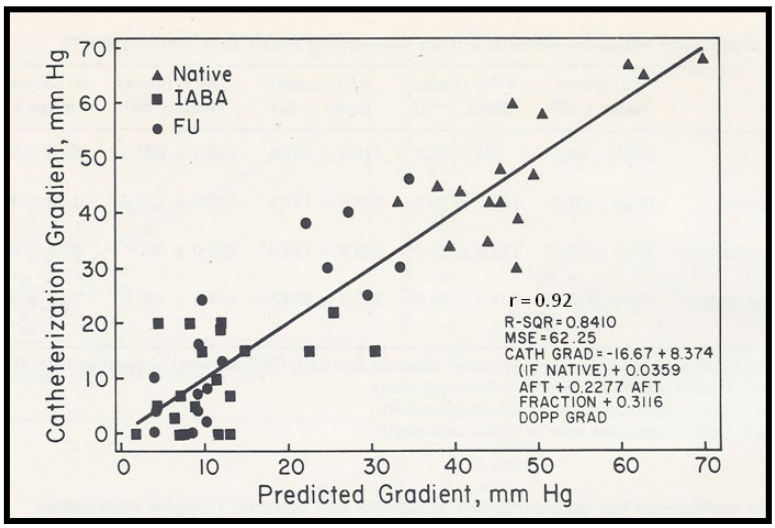


**Figure 2-13.** Linear regression analysis of catheterization-measured peak-to-peak gradients across aortic coarctation and predicted gradient calculated by the formula shown in the text indicated a better correlation (r = 0.92). Filled triangles: native coarctations; filled squares: coarctations immediately after balloon angioplasty (IABA); filled circles: coarctations at follow-up (FU). Reproduced from Rao PS, Carey P, Am Heart J 1989; 118:299-301.

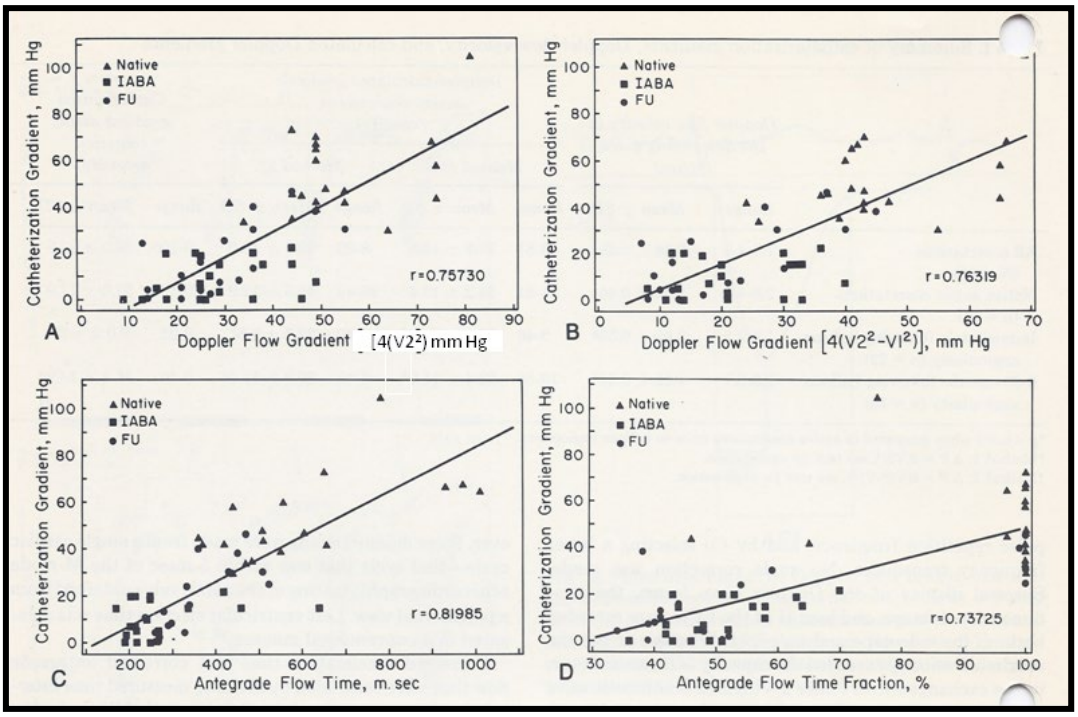


**Figure 2-14.** Linear regression analysis of catheterization-measured peak-to-peak and Doppler-derived (modified Bernoulli equation) peak instantaneous gradients across aortic coarctation are shown in A and B. Note the similar correlation coefficients irrespective of the inclusion of proximal Doppler velocities. Similar regression analysis of catheterization-measured peak-to-peak gradients and antegrade flow time (milli seconds) (C) and antegrade flow time fraction (%) (D) shows minimal increase in correlation coefficient (r = 0.82) when antegrade flow time is used. Filled triangles: native coarctations; filled squares: coarctations immediately after balloon angioplasty (IABA); filled circles, coarctations at follow-up (FU). Reproduced from Rao PS, Carey P, Am Heart J 1989; 118:299-301.

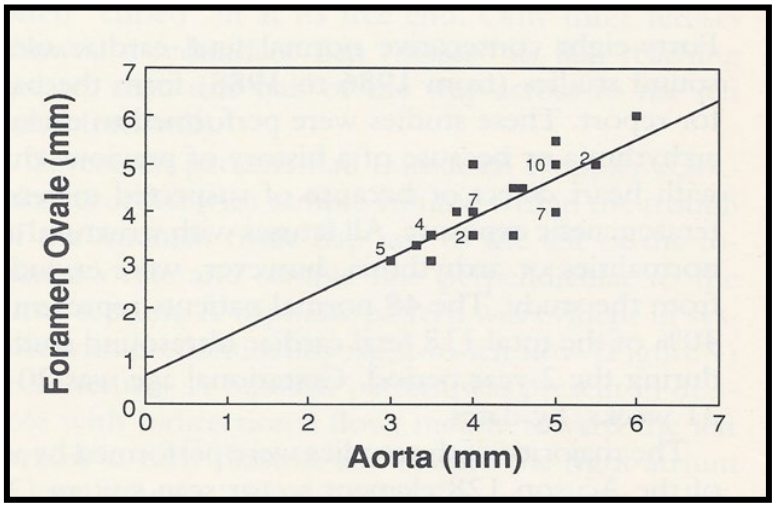


**Figure 2-15.** Plot of the diameter of the foramen ovale against the diameter of the aorta. The numbers indicate the number of subjects with that particular measurement. Note the excellent correlation with an r value of 0.84, y intercept of 0.605 and slope of 0.817. Reproduced from Wilson AD, Rao PS, Aeschlimann S, J Am Soc Echocard 1990; 3:491-4.

## Simple and Multiple Linear Regression Analysis

Simple and multiple linear regression was used to assess the relationship between independent variables, such as age, catheter size and various indices of arterial pulse and limb growth.[26] Contingency tables were prepared at arbitrary cut-off points to discern differences in arterial insufficiency and limb growth.[26] A similar analysis with contingency tabulation of balloon inflation characteristics was helpful in the evaluation of the effectiveness of balloon pulmonary valvuloplasty.[27,28] Multiple linear regression was also used to assess the relation between the independent main and interactive effects of stretch and recoarctation status and outcomes of gain and recoil.[29]

### Inter-Observer and Intra-Observer Variability

Inter-observer variability (measurements made by two or more observers examining the same data) and intra-observer variability (measurements made by the same observer at different times) were evaluated; a low percentage of variation assures the validity of the observations.

## Aortic Remodeling Following Balloon Angioplasty of Aortic Coarctation

When we examined aortic remodeling following balloon angioplasty of aortic coarctation, we had to employ special methods to assess this issue.[30] Inter- and intra-group comparisons of the shape of the aorta were needed for this process. Initially, measurements of the ascending aorta, isthmus, coarcted segment, and descending aorta immediately distal to the site of coarctation and at the level of the diaphragm (Figure 2-16) were made before angioplasty and at follow-up. For this assessment, it seemed appropriate to standardize the measurements to create a pure measure of shape. This was done by dividing each of the five aortic measurements by their average for each subject, before and after treatment. The resulting standardized measures would be on the same scale for each subject at each time point (Figure 2-17). Once the standardized aortic measures were determined, the variance (the sum of the squared differences of each measure divided by the degrees of freedom) from norm or unity was determined for each patient before balloon angioplasty and at the follow-up study. Inter- and intra-group comparisons were made by using the variance of five standardized diameter values. This method was designed to assess how much the aorta deviated from the norm (an aorta with a uniform diameter throughout). The test statistic for the intergroup comparison was the nonparametric Mann-Whitney U statistic. To test for the effect of balloon angioplasty within each group, Wilcoxon's signed rank test was used. The data (Figure 2-18) suggest that group A (good results) and group B (poor results) were not statistically different ($p > 0.05$) before angioplasty, though the variability of the aortic diameters in group B tended to be greater. At the follow-up study, the aortic measurements from group A patients were significantly more uniform ($p = 0.01$), suggesting a better remodeling in these patients with good results. There was improvement within both groups after angioplasty ($p < 0.05$); there was a greater percentage improvement (0.233 versus 0.057) in the group A patients than in the group B patients (0.287 versus 0.129). Cluster analysis was used to determine whether patients with good results could be differentiated from those with poor results on the basis of the shape of the aorta. Using Anderberg's "nearest centroid sorting" method with the variance of the standardized diameter values as the defining characteristic, the subjects were sorted into two clusters before and after treatment. In examining the 2 x 2 tables of clusters and groups, it is apparent that cluster analysis does not distinguish between groups A and B before angioplasty (meaning that both groups are similar) as well as it does at follow-up study. Inspection of schematic diagrams of the aorta (Figure 2-19) graphically indicates that there was a definite remodeling of the aorta in group A (with good intermediate-term follow-up results), whereas there was less remodeling in group B with poor and fair results (Figure 2-20).[30]

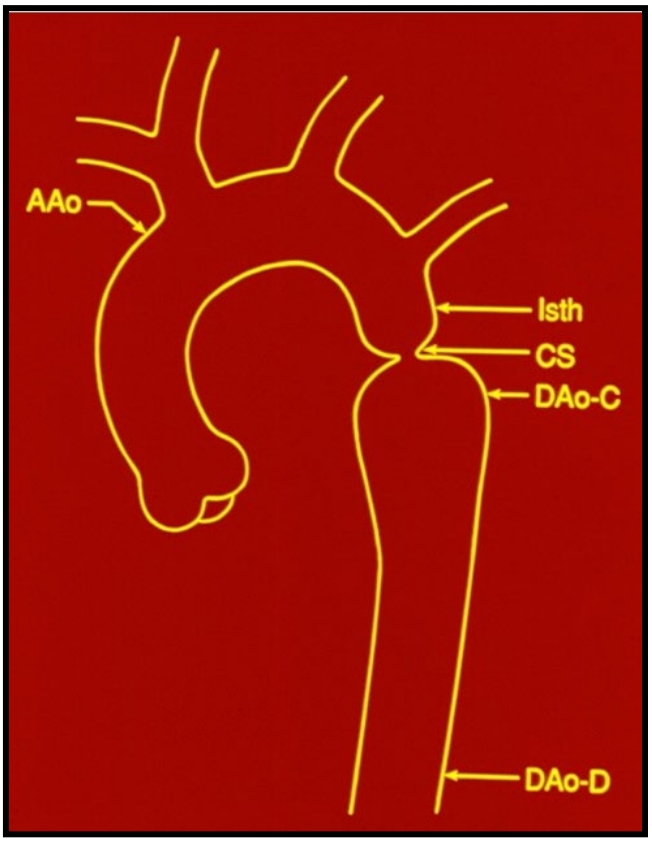


**Figure 2-16**. The diagram shows measurements of the aorta at five sites: the ascending aorta proximal to the origin of the right innominate artery (AAo), the isthmus (Isth), the coarcted aortic segment (CS), and the descending aorta distal to the coarctation (DAo-C) and at the level of the diaphragm (DAo-D). These measurements were made on the angiograms performed prior to balloon angioplasty and at follow-up, to determine the extent to which remodeling of the aorta had occurred. The measurements were made in two angiographic views, corrected for magnification and averaged. Modified from Rao PS, Carey P, J Am Coll Cardiol 1989; 14:1312-7.

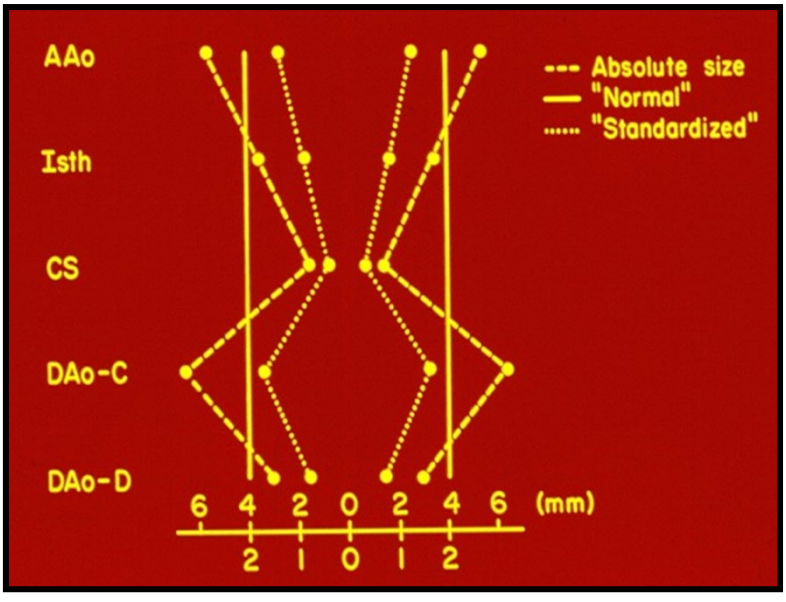


**Figure 2-17**. The diagram shows how the standardized diameters of the aorta at the five locations were calculated for each case before angioplasty and at follow-up study. The absolute sizes (dashed line) at each of the five locations were averaged; the averages are represented by solid lines. The standardized aortic measurement of each site is calculated by dividing the absolute size by the average of all five measurements. The dotted line represents the aortic shape, which can be compared with that of other patients and after intervention. Abbreviations are same as those used in Figure 2-16. Modified from Rao PS, Carey P, J Am Coll Cardiol 1989; 14:1312-7.

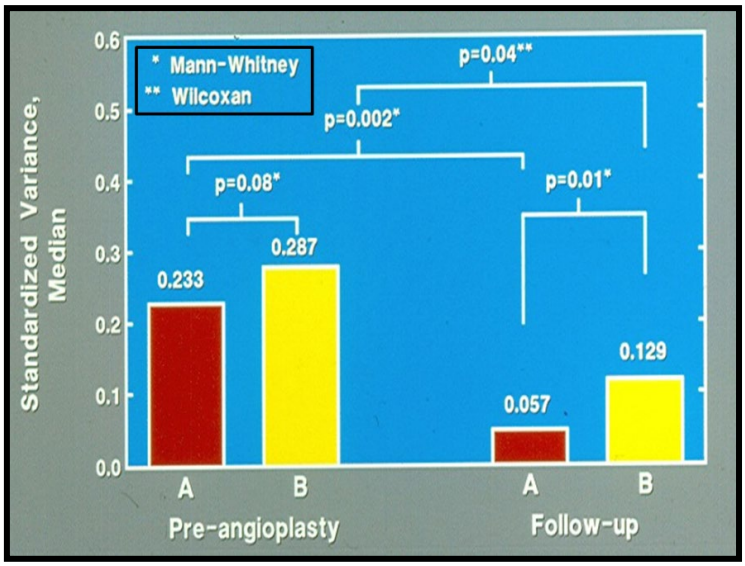


**Figure 2-18.** Bar graph showing comparison of the variances of standardized aortic diameters between groups A (good results) and B (poor results). The variance was similar (0.233 vs. 0.287; $p > 0.05$) in both groups before angioplasty. However, at follow-up the variances were different (0.057 vs. 0.129; $p = 0.01$). There was also a greater percentage improvement at follow-up study (0.233 vs. 0.057; $p = 0.002$) in group A, which had good results, than in group B which had fair or poor results (0.287 vs. 0.129; $p = 0.04$). The type of nonparametric test used for comparison is denoted in the insert at the left upper corner.

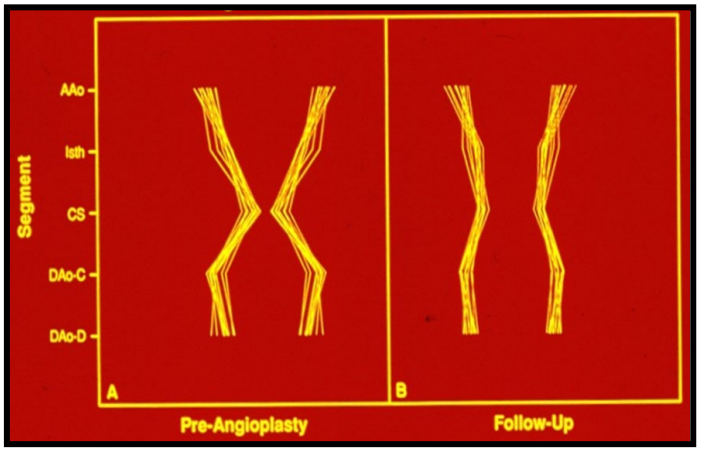


**Figure 2-19.** Schematic diagram of standardized aortic diameters pre-angioplasty (A) and at follow-up (B) in group A, which had good results. Note the improvement in that there is more uniformity of the various diameters of the aorta. Abbreviations are same as those used in Figures 2-16 & 2-17. Modified from Rao PS, Carey P, J Am Coll Cardiol 1989; 14:1312-7.

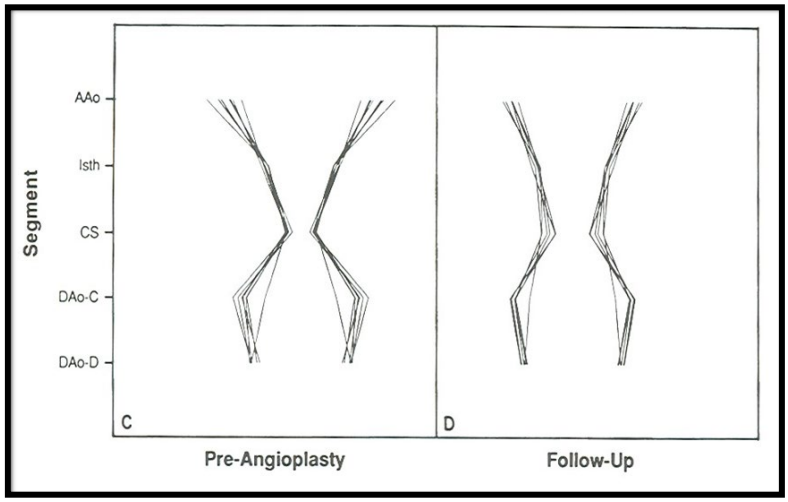


**Figure 2-20.** Schematic diagram of standardized aortic diameters pre-angioplasty (C) and at follow-up (D) in group B, which had poor results. Note that there is no significant improvement in the diameters of the aorta. Abbreviations are same as those used in Figures 2-16 & 2-17. Reproduced from Rao PS, Carey P, J Am Coll Cardiol 1989; 14:1312-7.

## References


1. Glanz SA. Primer of Biostatistics New York, McGraw Hill Book Company, Inc. 1981
2. Rao PS, Thapar MK, Kutayli F. Causes of restenosis following balloon valvuloplasty for valvar pulmonic stenosis. Am J Cardiol 1988; 62:979-82.
3. Rao PS, Thapar MK, Kutayli F, Carey P. Causes of recoarctation following balloon angioplasty of unoperated aortic coarctations. J Amer Coll Cardiol 1989; 13:109-15.
4. Rao PS, Thapar MK, Wilson AD, et al. Intermediate-term follow-up results of balloon aortic valvuloplasty in infants and children with special reference to causes of restenosis. Am J Cardiol 1989; 64:1356-60.
5. Rao PS. Causes of restenosis following balloon angioplasty/valvuloplasty: A review. Pediatr Rev Commun 1990; 4:157-72.
6. Rao PS, Koscik R. Validation of risk factors in predicting recoarctation following initially successful balloon angioplasty for native aortic coarctation. Am Heart J 1995; 130:116-21.
7. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association. 1958; 53:457-81.
8. Rao PS, Galal O, Patnana M, et al. Results of three-to-ten-year follow-up of balloon dilatation of the pulmonary valve. Heart 1998; 80:591-5.
9. Rao PS, Galal O, Smith PA, Wilson AD. Five-to-nine-year follow-up results of balloon angioplasty of native aortic coarctation in infants and children. J Am Coll Cardiol 1996; 27:462-70.
10. Galal O, Rao PS, Al-Fadley F, Wilson AD. Follow-up results of balloon aortic valvuloplasty in children with special reference to causes of late aortic Insufficiency. Am Heart J 1997; 113:418-27.
11. Rao PS, Sideris EB, Hausdorf G, et al. International Experience with Secundum Atrial Septal Defect Occlusion by The Buttoned Device. Am Heart J 1994; 128:1022-35.
12. Rao PS, Berger F, Rey C, et al. Results of transvenous occlusion of secundum atrial septal defects with 4$^{th}$ generation buttoned device: Comparison with 1$^{st}$, 2$^{nd}$ and 3$^{rd}$ generation devices. J Am Coll Cardiol 2000; 36:583-92.
13. Rao PS, Sideris EB. Centering-on-demand buttoned device: Its role in transcatheter occlusion of atrial septal defects. J Intervent Cardiol 2001; 14:81-9.
14. Rao PS, Kim SH, Choi J, et al. Follow-up results of transvenous occlusion of patent ductus arteriosus with buttoned device. J Am Coll Cardiol 1999; 33:820-6.
15. Rao PS, Kim SH, Rey C, et al. Results of transvenous buttoned device occlusion of patent ductus arteriosus in adults. Am J Cardiol 1998; 82:827-9.
16. Sideris EB, Rao PS. Buttoned device occlusion of patent ductus arteriosus. Current Intervent Cardiol Reports 3:71-79, 2001.
17. Grunkemeier GL, Thomas DR, Starr A. Statistical considerations in the analysis and reporting of time-related events. Application to analysis of prosthetic valve-related thromboembolism and pacemaker failure. Am J Cardiol 1977; 39:257-8.
18. Grunkemeier GL, Starr A. Actuarial analysis of surgical results: rationale and method. Ann Thorac Surg 1977; 24:404-8.
19. Rao PS, Solymar L, Mardini MK, et al. Anticoagulant therapy in children with prosthetic valves. Ann Thorac Surg 1989; 47:589-92.
20. Solymar L, Rao PS, Mardini MK, et al. Prosthetic valves in children and adolescents. Am Heart J 1991; 121:557-68.
21. Rao PS, Solymar L, Fawzy ME, Guinn G. Reassessment of usefulness of porcine heterografts in mitral position in children. Pediat Cardiol 1991; 12:164-69.
22. Rao PS, Thapar MK, Haggard RJ and Strong WB. Left ventricular muscle mass by m-mode echocardiography in children. J Cardiovasc Ultrasonography 1983; 2:381-9.
23. Rao PS. Doppler ultrasound in the prediction of transvalvar pressure gradients in patients with valvar pulmonic stenosis. International J Cardiol 1987; 15:195-203.
24. Rao PS. Carey P. Doppler ultrasound in the prediction of pressure gradients across aortic coarctation. Am Heart J 1989; 118:299-301.
25. Wilson AD, Rao PS, Aeschlimann S. Normal fetal foramen flap and transatrial Doppler velocity pattern. J Am Soc Echocard 1990; 3:491-4.
26. Lee HY, Reddy SCB, Rao PS. Evaluation of superficial femoral artery compromise and limb growth retardation following transfemoral artery balloon dilatations. Circulation 1997; 95:974-80.
27. Rao PS. Balloon pulmonary valvuloplasty: A review. Clin Cardiol 1989; 12:55-72.
28. Rao PS. Balloon angioplasty and valvuloplasty in infants, children and adolescents. Current Problems in Cardiology. YearBook Medical Publishers, Inc. Chicago, 1989; 14(8):417-500.
29. Rao PS, Waterman B. Relation of biophysical response of coarcted aortic segment to balloon dilatation with development of recoarctation following balloon angioplasty of native coarctation. Heart. 1998; 79: 407-411.
30. Rao PS, Carey P. Remodeling of the aorta following successful balloon coarctation angioplasty. J Am Coll Cardiol. 1989; 14:1312-7.

# CHAPTER 3

# PHYSIOLOGICALLY ADVANTAGEOUS VENTRICULAR SEPTAL DEFECTS

## Introduction

Spontaneous closure of isolated ventricular septal defects (VSDs) was well documented in the 1960s.[1-3] Even large VSDs causing congestive heart failure and/or requiring pulmonary artery banding to control heart failure during infancy have been reported to close spontaneously.[4-6] If the VSD is a part of complex cardiac defect, an open VSD may be important in maintaining suitable intra-cardiac shunt; such defects have been named as physiologically advantageous VSDs.[7] While spontaneous closure of isolated VSDs has been well documented, as mentioned above,[1-3] spontaneous closure of physiologically advantageous VSDs has not been studied as extensively as that of isolated VSDs.

## Initial Observations

The author's early observations consisted of two cases in which we documented spontaneous closure of physiologically advantageous VSDs;[7] one with tricuspid atresia and the other with double outlet right ventricle. In the first case, with tricuspid atresia, a VSD was documented by a holosystolic murmur on auscultation as well as by selective left ventricular angiography (Figure 3-1) at the age of 5.5 months. The patient was lost to follow-up and, upon re-evaluation at the age of 2.5 years, no holosystolic murmur was detected. While waiting for a systemic aorto-pulmonary shunt, the child had a hypoxic spell and died. Autopsy findings (Figure 3-2) revealed no evidence of a VSD.

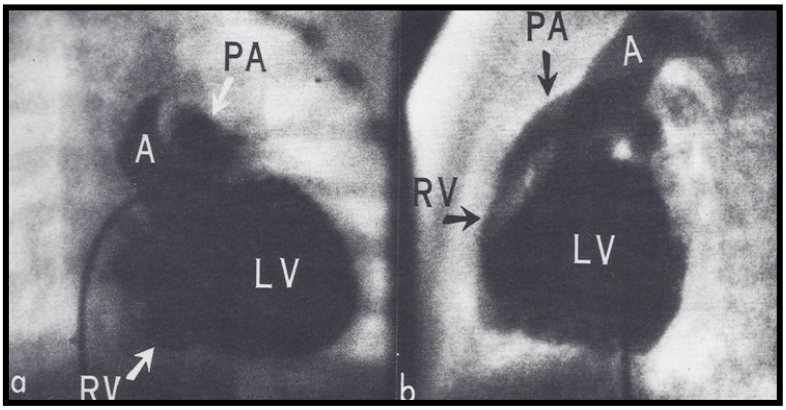


**Figure 3-1**. Selective left ventricular (LV) cineangiogram in antero-posterior (a) and lateral (b) views at the age 5.5 months, demonstrating opacification of the right ventricle (RV) via a ventricular septal defect (not labeled). A, aorta; PA, pulmonary artery. Reproduced from Rao PS, Sissman NJ, Circulation 1971; 43:83-90.

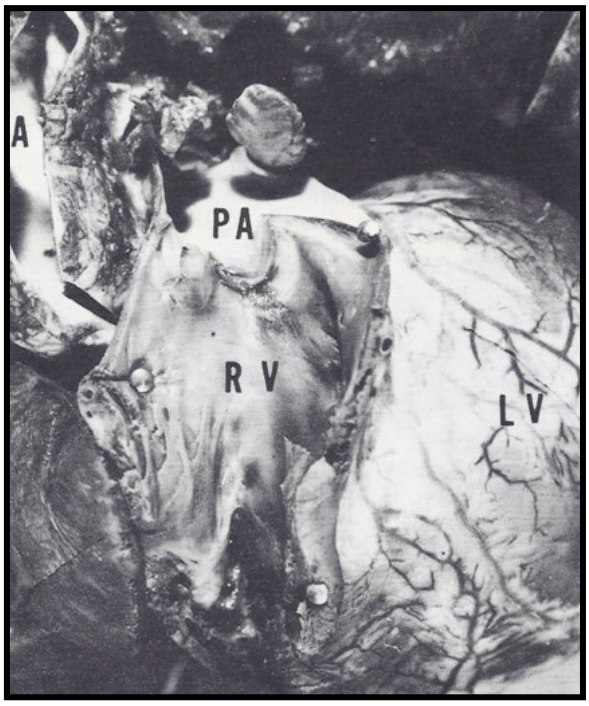


**Figure 3-2.** Photograph of the heart with the right ventricle (RV) open at autopsy at the age of 2.5 years, demonstrating no evidence of the previously seen (Figure 3-1) ventricular septal defect. A, aorta; PA, main pulmonary artery. Reproduced from Rao PS, Sissman NJ, Circulation 1971; 43:83-90.

In the second case, with double outlet right ventricle, a VSD was documented at the age of 3 months by a holosystolic murmur on physical examination and by selective left ventricular angiography.[7] Palliative surgical intervention was recommended, but the parents refused to consent for surgery. The patient reappeared at the age of 2.5 years with severe hypoxemia and congestive heart failure. Again, surgery was recommended, but before any surgery could be performed, the infant was found dead in his crib. The autopsy confirmed the diagnosis of double outlet right ventricle and the VSD was found to be almost completely closed (Figure 3-3).


**Figure 3-3.** Photographs of the heart of the child with double outlet right ventricle (RV) demonstrating closure of the ventricular septal defect (VSD). a. View from the right ventricular aspect shows a very small remaining opening of the VSD (black arrow). b. Photograph from the right atrial aspect illustrating that the VSD is entirely covered by the septal leaflet of the tricuspid valve; the bright central area is because of the light transmitted through the translucent tricuspid valve leaflet. The VSD measured 1.0 X 1.0 cm in size. c. Photograph from the left ventricular (LV) side shows that the VSD is completely closed; the arrow points to strands of thickened endocardium covering the VSD. A, aorta; PA, pulmonary artery; TV, tricuspid valve leaflets; MV, mitral valve leaflet. Reproduced from Rao PS, Sissman NJ, Circulation 1971; 43:83-90.

These observations prompted the author to focus on the issue of spontaneous closure of physiologically advantageous VSDs in tricuspid atresia.[8-13] We have thoroughly studied this matter in patients with tricuspid atresia which resulted in documenting functional,[8] partial and complete[9-13] VSD closures.

## Functional VSD Closure

Following the documentation of spontaneous closure of physiologically advantageous VSDs as described above,[7] we had the opportunity to observe two infants with tricuspid atresia with normally related great arteries who had functional VSD closure.[8] In both infants the VSD was shown to be open by the presence of loud holosystolic

murmurs, and by left ventricular cineangiography (Figure 3-4). The murmur was heard at the time of angiography and during subsequent clinical evaluations. However, during the episodes of hypercyanotic spells, the murmur of the VSD could not be heard (by several observers); yet, at autopsy examination, the VSDs were present, though small in size (Figure 3-5). This led us to the conclusion that the VSD was functionally closed during the hypercyanotic spells.

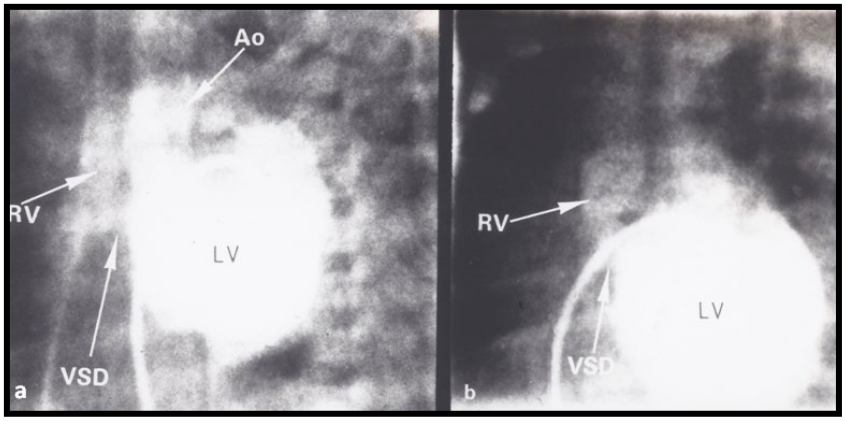


**Figure 3-4.** Selected frames of left ventricular (LV) cineangiograms in left anterior oblique (a) and posterio-anterior (b) views demonstrating ventricular septal defect (VSD) with opacification of the right ventricle (RV). Ao, aorta. Reproduced from Rao PS, et al., Am J Dis Child 1974; 127:36-40

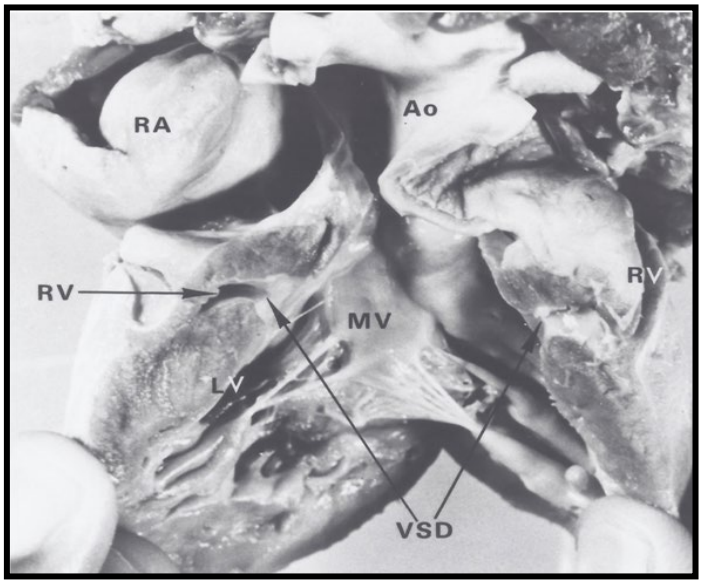


**Figure 3-5.** Photograph of the heart of the case described in figure 3-4 demonstrating the ventricular septal defect (VSD) (long arrows). The cardiac specimen was cut at the level of the ventricular septum. Thick muscular tissue is seen surrounding the VSD. The small right ventricle (RV) (smaller arrow) is also shown. Ao, aorta; LV, left ventricle; MV, mitral valve; RA, right atrium. Reproduced from Rao PS, et al., Am J Dis Child 1974; 127:36-40.

A third case was presented to demonstrate that the obstruction to pulmonary blood flow is at the level of the VSD in cases of tricuspid atresia with normally related great arteries. (Pressure pullback tracings from the pulmonary artery to the right ventricle and then into the left ventricle [across the VSD] showed a severe systolic pressure gradient between the ventricles.) Our own observations in these cases, as well those made as by others,[14] indicated that the VSD in tricuspid atresia cases is located in the muscular septum, completely surrounded by muscular tissue. Consequently, it is feasible to fully occlude the VSD by the contraction of the ventricular septal muscle. The mechanisms for spontaneous closure are not known, but the mechanisms for developing hypercyanotic spells may be similar to those postulated for tetralogy of Fallot. We also suggested that the acute management of such spells should be similar to that for the cyanotic spells in tetralogy of Fallot: by administering oxygen, morphine and beta-blockers, followed by aorto-pulmonary shunt. A brief discussion of available surgical options, based on the state-of-the-art surgery in the mid-1970s, was also included in our paper.[8] It was concluded that increased cyanosis, along with the disappearance or decreased intensity of a previously auscultated murmur in patients with complex congenital heart disease, should arouse suspicion of functional closure of physiologically advantageous VSDs.[8]

## Anatomic (Partial and Complete) VSD Closure

Continuing the quest to further uncover the significance of spontaneous closure of physiologically advantageous VSDs in tricuspid atresia, the clinical, angiographic, and pathological features of 20 consecutive cases of tricuspid atresia were analyzed;[9] complete closure was documented in three cases, while partial closure was seen in another three patients. Five of the VSD closures were documented among the sixteen case of type I (normally related great arteries) and in one of the four cases of type II (transposition of the great arteries). Detailed case histories and findings in all six cases with VSD closure were presented.[9] Progressive cyanosis, disappearance of a previously heard murmur and polycythemia (Figure 3-6) were seen; these findings were more noticeable in cases of complete VSD closure than in those of partial closure. Progressive decreases in cardiac size and pulmonary vascular markings were also observed (Figure 3-7). Cine-angiographic frames demonstrating the VSD (Figure 3-8) and corresponding pathologic specimen (Figure 3-9) showing VSD closure were presented to illustrate spontaneous VSD closure.[9] For further details of the other cases, the reader is referred to the British Heart Journal paper.[9] Pathologic findings indicated progressive muscular "encroachment" of the margins of the VSDs with ensuing fibrosis and covering by endocardial proliferation as a likely mechanism of closure.

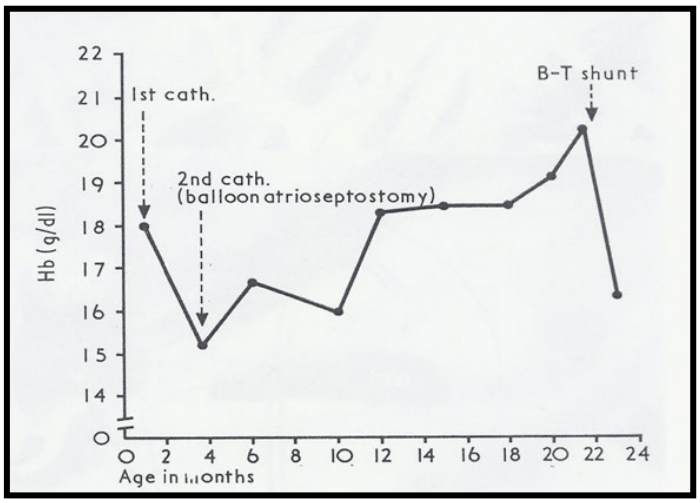


**Figure 3-6.** Hemoglobin values in one case with complete VSD closure were plotted against the age of the baby in months. Following a normal drop in hemoglobin during early infancy, a progressive increase in hemoglobin was noted, as the ventricular septal defect constricted. Following a Blalock-Taussig (B-T) shunt, the hemoglobin decreased. Reproduced from Rao, PS, Br Heart J 1977: 39:276-88.

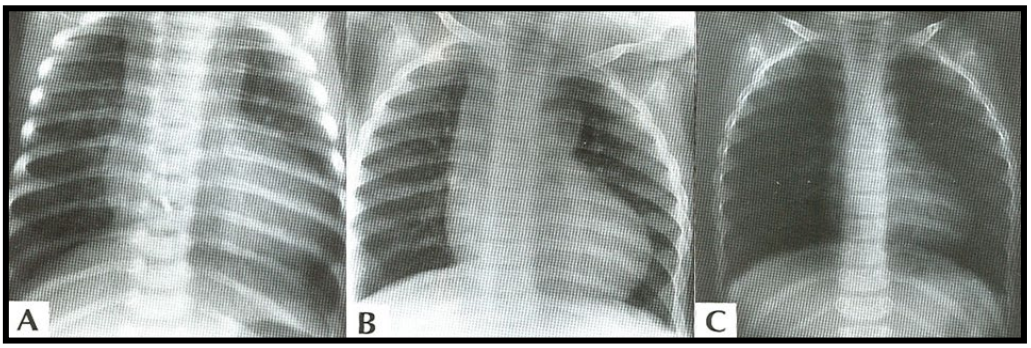


**Figure 3-7.** Serial chest X-rays in a tricuspid atresia patient with progressive diminution of the size of the ventricular septal defect, demonstrating a decrease in the size of the heart and of the pulmonary vascular marking. Reproduced from Reference 10.

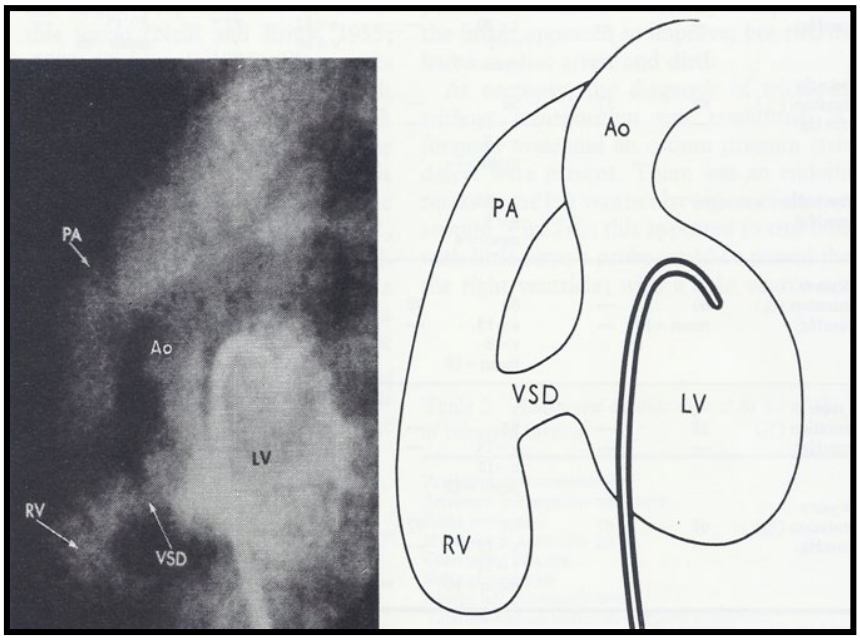


**Figure 3-8**. Selected cine frames from left ventricular (LV) angiogram in straight lateral view in a patient with Type I tricuspid atresia, demonstrating a moderate-sized ventricular septal defect (VSD) in the muscular ventricular septum. Ao, aorta; PA, pulmonary artery; RV, right ventricle Reproduced from Rao, PS, Br Heart J 1977: 39:276-88.

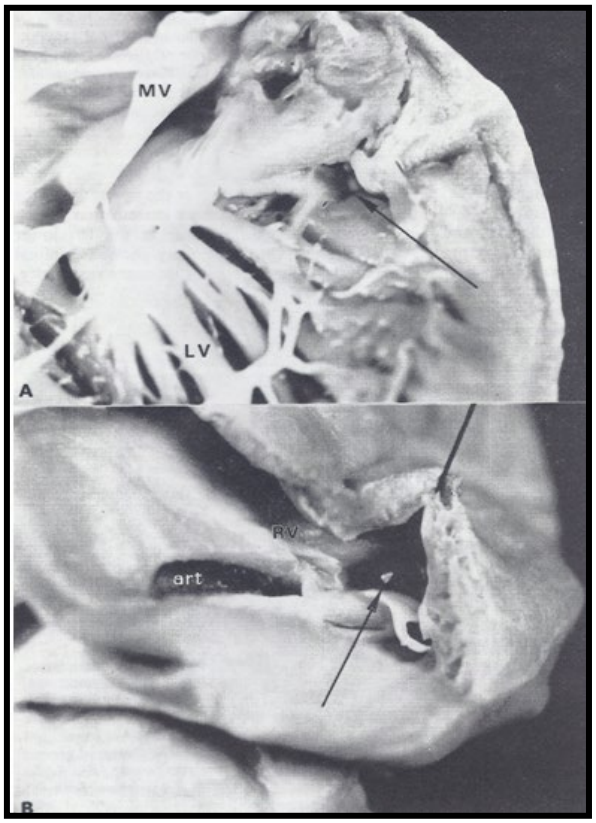


**Figure 3-9.** Photographs of the heart of the infant presented in figure 3-8 demonstrating closure of the ventricular septal defect. A. Left ventricle (LV) showing an endocardial recess (arrow) ending blindly. When a probe was passed to explore this region, the probe passed into the right ventricle (RV), via the closed ventricular septal defect. B. Right ventricular aspect is shown after the removal of the probe. The arrow shows a shiny opening created by the probe. Also, note a very small RV. art, artifact; MV, mitral valve. Reproduced from Rao, PS, Br Heart J 1977; 39:276-88.

The frequency of VSD closure in cases of tricuspid atresia was 38% and was not too dissimilar to that of spontaneous closure of isolated VSDs. The causes of VSD closures are unknown and it was observed that these VSD closures were not started nor hastened by the surgical shunts that these patients had. The therapeutic implications of the VSD closures in tricuspid atresia were emphasized: 1. Babies with spontaneous closure of VSD in type I tricuspid atresia

are likely to require a Blalock-Taussig type of shunt earlier than otherwise required, 2. The Blalock-Taussig type of shunt is preferable to the classic Glenn shunt (the concept of the bidirectional shunt has not been developed as of 1977), because the left pulmonary circuit will be without blood flow should the VSD close, and 3. In type II tricuspid atresia cases, the presence of a non-restrictive VSD is critical for a successful Fontan operation. Consequently, the size of the VSD should be assessed at the time of Fontan surgery. If the VSD is small, enlargement of the VSD or a complete bypass of the VSD and right ventricle (Figure 7 of reference 9) is important.[9]

## Additional Observations on Spontaneous VSD Closures in Tricuspid Atresia

Our interest in spontaneous closure of physiologically advantageous VSDs continued; the phenomenon was reviewed in book chapters,[10,11] original papers[12,13] and editorial communications.[15-17] In the book chapters and original papers[10-13] a review of the literature and the analysis of a larger number of tricuspid atresia patients than in our prior publication[9] was undertaken. The study subjects included 40 consecutive tricuspid atresia patients seen between 1965 and 1980 at the Medical College of Georgia Hospitals. Thirty-one patients were of Type I (normally related great arteries), eight patients were of Type II (d-transposition of the great arteries) and one was of type IV (truncus arteriosus).[18]

Spontaneous closure of the VSD was documented in 11 of the 31 Type I patients; closure was complete in eight and partial in three. The clinical expression of spontaneous closure of the VSD in Type I patients was progressive cyanosis, rising hemoglobin and hematocrit and/or disappearance of a previously heard cardiac murmur. The evidence for VSD closure was suggested by clinical features (disappearance of a previously heard murmur and progressive cyanosis), decreasing size of the heart and pulmonary vascular marking on chest X-ray, and increasing levels of hemoglobin. It was documented by angiography, surgical and/or pathologic inspection.[10-13]

Three of the eight Type II patients exhibited partial closure of the VSD; no complete closures were documented in this group. The evidence for VSD closure was the development of a pressure gradient across the VSD, the diminished size of the VSD, or both, which was documented by cardiac catheterization and angiography (Figure 3-10).[10-13]

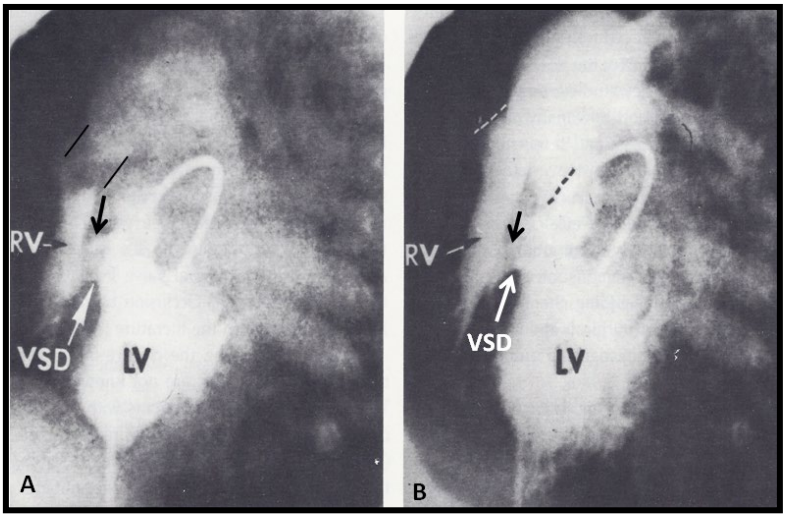


**Figure 3-10.** Selected cine frames of left ventricular (LV) angiograms in left anterior oblique view of a patient with Type II tricuspid atresia at one week (A) and eight months (B) of age. The right ventricle (RV) and aorta were opacified via a ventricular septa1 defect (VSD) (arrow). The pulmonary artery was opacified directly from the LV. The margins of the VSD were marked with black arrows at the top and white arrows at the bottom. In A the size of the VSD is similar to the diameter of the aorta while in B the VSD is about one-third to one-half the size of the aorta (the aortic root is demarcated in both A and B for clarity). Cardiac catheterization during B revealed a 25 mmHg peak-systolic pressure gradient between the RV and LV across the VSD. Modified from Rao PS, Ann Thorac Surg 1983; 35:121-31.

In the discussions that followed, an extensive review of the literature up to that time was undertaken, and age and sex incidence of VSD closure, mechanisms of VSD closure, factors influencing VSD closure, and surgical implication of VSD closure were discussed.[10-13]

## Review of the Literature up to Early 1980s

Spontaneous closure of the VSD in Type I tricuspid atresia (with normally related great arteries), both complete and partial, has been reported in prior studies and the clinical features in these studies are similar to those described in our studies, as detailed in the author's previous publications.[9-13] While the obstructive nature of the VSD in Type II