

Advances in Experimental Medicine and Biology 1441

Silke Rickert-Sperling  
Robert G. Kelly  
Nikolaus Haas *Editors*

# Congenital Heart Diseases: The Broken Heart

Clinical Features, Human Genetics and  
Molecular Pathways

*Second Edition*

 Springer

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# **Advances in Experimental Medicine and Biology**

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## Foreword of the 1st Edition

As is indicated in its title, the book you are about to read is concerned with the congenitally malformed heart. Approximately eight neonates in every thousand born alive present with such a “broken heart”. This number has changed little since Maude Abbott, when describing the first plate in her Atlas devoted to congenitally malformed hearts, commented that “An understanding of the elementary facts of human and comparative embryology is essential to an intelligent grasp of the ontogenetic problems of congenital cardiac disease”. Paul Dudley White, when writing the foreword to her Atlas, commented that it had been left to Abbott to “make the subject one of such general and widespread interest that we no longer regard it with either disdain or awe as a mystery for the autopsy table alone to discover and to solve”. It is perhaps surprising, therefore, to realise that it has taken nearly a century for us to achieve the necessary understanding of the “elementary facts” emphasised by Abbott. Indeed, it is not that long since, in company with my very good friend and collaborator Anton Becker, we suggested that interpretations based on embryology might prove to be a hindrance, rather than a help, in understanding the congenitally malformed heart. The contents of this book show how much has changed in the years that have passed since we made that comment, such that we now need to eat our words.

As is revealed by the multiple chapters of this book, the recent advances made in the fields of cardiac embryology and molecular genetics have been truly spectacular. It was these fields that were expertly summarised in the volumes edited by Rosenthal and Harvey. The details contained in the central part of this book, related to central molecular pathways, recapitulate and extend those reviews. Such extensive knowledge of the genetic and molecular background, however, is of limited value if these interpretations cannot properly be translated into the findings observed on a daily basis by those who diagnose and treat the individual cardiac lesions. The first part of this book, therefore, provides a necessarily brief overview of normal cardiac development, while the final chapters then incorporate the developmental and molecular findings into the clinical manifestations of the abnormal morphogenesis.

I know from my own experience how difficult it is to obtain such chapters from multiple authors, who nowadays are themselves under greater pressure to produce primarily in the peer-reviewed realm. The editors, therefore, are to be congratulated on assembling such a panoply of authoritative texts. As might be expected, not all of

the texts are of comparable length or content. The critical reader will note that several of the topics addressed remain contentious, and that opinions continue to vary between the chosen experts. This is no more than to be expected, since the topics remain very much moving targets. One hopes, therefore, that this is but the first edition of a work which itself, for the first time, seeks to provide in detail the scientific background to the specific lesions that continue to break the normal heart. As the pages of this book demonstrate, we still have much to do if we are fully to understand the mechanics of normal as opposed to abnormal cardiac development.

London, UK  
August 2015

Robert H. Anderson

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## Foreword of the 2nd Edition

It has been now 8 years since the publication of the first edition of “The Broken Heart”. In writing the foreword to the first edition, I cited the importance placed by Maude Abbott, certainly the first, if not the most influential, of dedicated pediatric cardiac morphologists, on an appreciation of normal cardiac development as the basis for understanding the anatomy of the congenitally malformed heart. It remains, of course, a firm grasp of the underlying anatomical substrate that underscores the correct diagnosis and treatment of the various phenotypes encountered when the heart is congenitally malformed. In continuing my foreword, I pointed to the time taken to achieve the necessary understanding of the elementary facts highlighted by Abbott. I then further emphasized how the contents of the first edition demonstrated the spectacular advances made in the fields of cardiac molecular genetics over the turn of the twenty-first century. Further improvements are now to be found in the revised chapters of this second edition.

In the first edition of the book, the important chapter on normal cardiac development had “necessarily been brief”. It has been markedly expanded in the second edition. In this regard, I should acknowledge my bias, since I am one of the co-authors of this chapter. Its importance, nonetheless, lies in the fact that it is based on a detailed analysis of temporal development of the human heart during the embryonic period. It matches a companion study of the same material now published in “Communications in Biology”, but accounts for the changes in systematic rather than longitudinal fashion. The two accounts are complementary. In my obviously biased opinions, I do believe that the chapter and its partner manuscript now provide all the material required to fulfill the expectations of Maude Abbott. Most importantly, it represents the necessary anatomical skeleton on which to assemble the extensive information provided in the central section of the book devoted to molecular and genetic advances. As the editors emphasize in their own preface, this central part has now also been expanded to include chapters on single-cell transcriptomics, stem cells, organoids, and cardiac metabolism. These initial parts of the book then set the scene for understanding the “meat” of the practice of pediatric cardiology, namely the clinical features, the underlying genetic alterations, the related animal models, and the molecular pathways of the different lesions that together make up congenital heart disease.

I have now been involved in the investigation of these various entities for more than half a century. It is encouraging to note that, slowly but surely, the controversies



that surrounded many of these lesions when I started in the field are being resolved. I commented on such controversies in my foreword to the first edition. I suggested that the topics remained as “moving targets”. Readers of this second edition will discover that, in the period between the editions, the targets have become much easier to hit. This reflects the ability, developed over the past decade, for clinicians to provide three-dimensional illustrations of the underlying anatomy by means of virtual dissection, or creation of models, of datasets obtained during life. These advances also receive appropriate emphasis in this second edition. The appearance of this second edition itself points to the success of the first edition, which provided in detail the scientific background to the specific lesions that continue to break the normal heart. As the pages of the second edition demonstrate, we continue to increase our understanding of the mechanics of normal as opposed to abnormal cardiac development.

London, UK  
July 2023

Robert H. Anderson

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## Preface

In the fifteenth century, Leonardo Da Vinci made the first drawing of partial anomalous pulmonary venous connection, and 300 years later, Karl von Rokitansky described ventricular septal defects. Since then, the understanding of congenital heart diseases (CHDs) has rapidly evolved, encompassing clinical recognition, therapeutic opportunities, and the exploration of their developmental and genetic origins.

The initial wave of progress focused on enhancing clinical diagnosis and therapy through anatomical, physiological, and surgical considerations. Consequently, the mortality rate for patients with CHD decreased to below 1 in 100,000 cases, giving rise to a new group of adult patients with corrected and palliated CHD.

The subsequent wave of progress shifted attention toward the developmental, genetic, and molecular aspects of CHDs. Valuable insights were gained by studying animal models alongside humans, leading to the discovery of numerous genes, signaling pathways, and other molecular and hemodynamic factors. The developmental perspective served as a crucial starting point for these investigations.

After decades of basic research primarily utilizing animal models, the focus has shifted toward the human phenotype. Technological advancements have overcome previous limitations, enabling the study of complex biological questions and systems. Additionally, there is a growing recognition that improving human health is a central aim of life science research. This book consolidates clinical, genetic, and molecular knowledge into a single volume, with a particular emphasis on the observed human phenotype during development and in the disease state. Its intended audience encompasses both basic scientists and physicians. Furthermore, it aims to contribute to the current third wave of progression, where the basic science of cardiovascular development is translated into clinical diagnosis and therapy of CHDs.

To achieve this goal, the book is structured into three main parts. The first part provides an introduction to the development of the heart and its vessels. The second part offers an overview of molecular pathways influencing the development of multiple cardiovascular structures. Lastly, the book adopts a textbook-like structure in the third part, focusing on different types of congenital heart diseases. Each chapter delves into their clinical features, underlying genetic alterations, related animal models, and pathways.

In this second edition, published eight years after the first edition, every chapter has been thoroughly updated to reflect the rapid pace of discovery and technological innovation in the field of CHD research. New chapters have been included, covering topics such as single-cell transcriptomics—a revolutionary approach that offers unprecedented insights into cellular heterogeneity and differentiation pathways. Stem cell and organoid approaches to study CHD are also discussed, as they accelerate mechanistic understanding and hold therapeutic potential. Additionally, cardiac metabolism has emerged as a highly dynamic driver of cardiac development and is explored in a dedicated chapter. Furthermore, the book presents the 3D-reconstruction of human heart development, showcasing both its beauty and complexity. Finally, the clinical chapters have been expanded significantly, incorporating additional pathological details and new illustrations. Each clinical chapter now features a section highlighting the diagnostic imaging approaches best suited for analyzing specific forms of CHD.

We extend our deepest gratitude to all the contributors to this volume, whose expertise and state-of-the-art accounts have enriched this book.

Berlin, Germany  
Marseille, France  
Rochester, MN, USA  
Munich, Germany  
April 2024

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## List of Abbreviations

22q11DS	22q11.2 deletion syndrome
A	Atrium
AAA	Aortic arch anomalies
ACTC1	Cardiac alpha-actin
ACVR	Activin A receptor
AD	Arterial duct
ADAM19	ADAM metallopeptidase domain 19
ADAR	Adenosine deaminase that acts on RNA
ADP	Adenosine diphosphate
AGS	Alagille syndrome
AICD	Automatic internal cardiac defibrillator
ALCAPA	Anomalous origin of the left coronary artery from the pulmonary artery
AKT	V-akt murine thymoma viral oncogene homolog
AngII	Angiotensin II
ANP	Atrial natriuretic peptide
ANK2	Ankyrin B
ANKRD1/CARP	Ankyrin repeat domain 1, cardiac muscle
Ao	Aorta
AP	Action potential
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ASD	Atrial septal defect
ATFB	Atrial fibrillation
ATP	Adenosine triphosphate
AV	Atrioventricular
AVB	Atrioventricular bundle
AVC	Atrioventricular canal
AVN	Atrioventricular node
AVSD	Atrioventricular septal defect
BA	Bulbus arteriosus
BAF	Brg1-associated factor
BAV	Bicuspid aortic valve
BBS	Bardet-Biedl syndrome

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BDM	2,3-butanedione monoxime
BET	Bromodomain and extra terminal
BMP	Bone morphogenetic protein
BNP	Brain natriuretic peptide
bpm	Beat per minutes
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BRG1	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4 (also known as brahma-related gene 1)
BRGDA	Brugada syndrome
BWIS	Baltimore Washington Infant Study
CAA	Coronary artery anomalies
CACN	Calcium channel, voltage-dependent, L type
CAD	Coronary atherosclerotic disease
CaMK	Calmodulin-dependent kinase
cAMP	Cyclic adenosine monophosphate
CALM	Calmodulin
CASQ	Calsequestrin
CAT	Common arterial trunk
CAVV	Common atrioventricular valve
CBP	CREB-binding protein
CC	Cardiac crescent
CCDC	Coiled-coil domain containing
CCS	Cardiac conduction system
CCV	Common cardiac vein
CCVA	Congenital coronary vascular anomalies
CF	Cephalic folds
CFC1	Cripto, FRL-1, Cryptic family 1 (CRYPTIC)
CFD	Computational fluid dynamics
CGH	Comparative genomic hybridization
CHARGE	Coloboma of the eye, <i>Heart</i> defects, <i>Atresia</i> of the nasal choanae, <i>Retarded</i> growth and/or development, <i>Genital</i> and/or <i>urinal</i> abnormalities, and <i>Ear</i> anomalies
CHD	Congenital heart disease/defect
CHD7	Chromodomain helicase DNA-binding protein 7
CHF	Congestive heart failure
ChIP	Chromatin immunoprecipitation
CITED2	Cbp/P300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain 2
CNCCs	Cardiac neural crest cells
CNV	Copy number variation
CoA	Celiac artery
CoA	Coarctation of the aorta
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CRE	Cre recombinase

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CRELD1	Cysteine-rich protein with EGF-like domains 1
CRISPR	Clustered regularly interspaced short palindromic repeats
CTD	Conotruncal defects
CTGF	Connective tissue growth factor
CTVM	Canine tricuspid valve malformation
CX	Connexin
DA	Dorsal artery
DCM	Dilated cardiomyopathy
DGC	Dystrophin-glycoprotein complex
DMP	Dorsal mesenchymal protrusion
DNA	Deoxyribonucleic acid
DNAH	Dynein, axonemal, heavy chain
DNMT	DNA methyltransferases
DORV	Double outlet right ventricle
dpf	Days post fertilization
DPF3	D4 Zinc and double PHD fingers family 3 (also known as Baf45c)
DSC2	Desmocollin 2
DSG2	Desmoglein 2
DSP	Desmoplakin
Dvl2	Disheveled segment polarity protein 2
E	Embryonic day
ECs	Endocardial cushions
ECG	Electrocardiogram
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
ELC	Essential myosin light chain
ELN	Elastin
EMT	Epithelial-to-mesenchymal transition
ENU	N-ethyl-N-nitrosourea
EPDC	Epicardially derived cells
EPO	Erythropoietin
ErbB	Erythroblastic leukemia viral oncogene homolog
ERK	Extracellular signal-regulated kinase
ERS	Early repolarization syndrome
ESC	Embryonic stem cells
ET1	Endothelin 1
EVC	Ellis-van-Creveld
FA	Folic acid
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FHF	First heart field
FHL1	Four and a half LIM domains protein 1

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FISH	Fluorescence in situ hybridization
FOX	Forkhead box
FOG2	Friend of GATA 2
GATA	GATA binding protein
GATA4	GATA-binding protein 4
GBX	Gastrulation brain homeobox
GDF1	Growth differentiation factor
GFP	Green fluorescent protein
GJA5	Gap junction protein, alpha 5, 40 kDa (connexin 40)
GPCR	G-protein coupled receptors
GRP	Gastrocoel roof plate
GWAS	Genome-wide association study
H3K4me3	Trimethylation of histone H3 at lysine 4
H3K4me2	Dimethylation of histone H3 at lysine 4
H3K4me1	Monomethylation of histone H3 at lysine 4
H3K24ac	Acetylation of histone H3 at lysine 24
H3K27ac	Acetylation of histone H3 at lysine 27
H3K27me3	Trimethylation of histone H3 at lysine 27
HAND	Heart and neural crest derivatives expressed
HAT	Histone acetyltransferase
HDAC	Histone deacetylase
HCM	Hypertrophic cardiomyopathy
HCN4	Hyperpolarization activated cyclic nucleotide-gated potassium channel 4
HE	Hematoxylin and eosin
HES1	Hes family BHLH transcription factor 1
HEY	Hes-related family bHLH transcription factor with YRPW motif
HH	Hamburger—Hamilton stage
HIF	Hypoxia-inducible factor
HLHS	Hypoplastic left heart syndrome
HOX	Homeobox genes
hpf	Hours post fertilization
HT	Heart tube
HV	Hepatic vein
IAA	Interrupted aortic arch
IC	Inner curvature
IGF1	Insulin-like growth factor 1
INO80	Inositol requiring 80
IP3	Inositol-1,4,5-triphosphate
IPCCC	International Pediatric and Congenital Cardiac Code
iPSCs	Induced pluripotent stem cells
IRX	Iroquois homeobox
ISL1	ISL LIM homeobox 1 (Islet 1)
IUGR	Intrauterine growth restrictions
IVC	Inferior caval vein

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IVF	Idiopathic ventricular fibrillation
IVS	Interventricular septum
JAG1	Jagged 1
JNK	c-Jun N-terminal kinase
JUP	Junctional plakoglobin
KLF	Krüppel-like factor
KLF2	Krüppel-like factor 2
KCNE	Potassium channel, voltage-gated subfamily E regulatory beta subunit
KCNJ	Potassium channel, inwardly rectifying subfamily J
KCNQ	Potassium channel, voltage-gated KQT-like subfamily Q
LA	Left atrium
LAL	Left atrial ligation
LAo	Left aortic arch
LBB	Left bundle branch
LCC	Left common carotid
LEFTY	Left-right determination factor
LEOPARD	<i>Lentigenes</i> , <i>ECG</i> conduction abnormalities, <i>Ocular hypertelorism</i> , <i>Pulmonic stenosis</i> , <i>Abnormal genitalia</i> , <i>Retardation of growth and sensorineural Deafness</i>
LIF	Leukemia inhibitory factor
LMNA	Lamin A/C
lncRNA	Long non-coding RNA
LPA	Left pulmonary artery
LPM	Lateral plate mesoderm
LLPM	Left lateral plate mesoderm
LPu	Left pulmonary artery
LQTS	Long QT syndrome
L-R	Left-to-right shunt
LRO	Left-right organizer
LSA	Left subclavian artery
LTCC	L-type calcium channel
LV	Left ventricle
LVNC	Left ventricular noncompaction
MAPCA	Major aortopulmonary collateral arteries
MBD	Methyl-CpG binding domain-based
MDM2	Murine double minute 2
MED13L	Mediator complex subunit 13-like
MEF2C	Myocyte enhancer factor 2C
MEK2	kinase 2
MERS	Middle east respiratory syndrome
MESP1	Mesoderm posterior 1 homolog
MHC	Myosin heavy chain
MI	Myocardial infarction
MMP	Matrix metalloproteinases