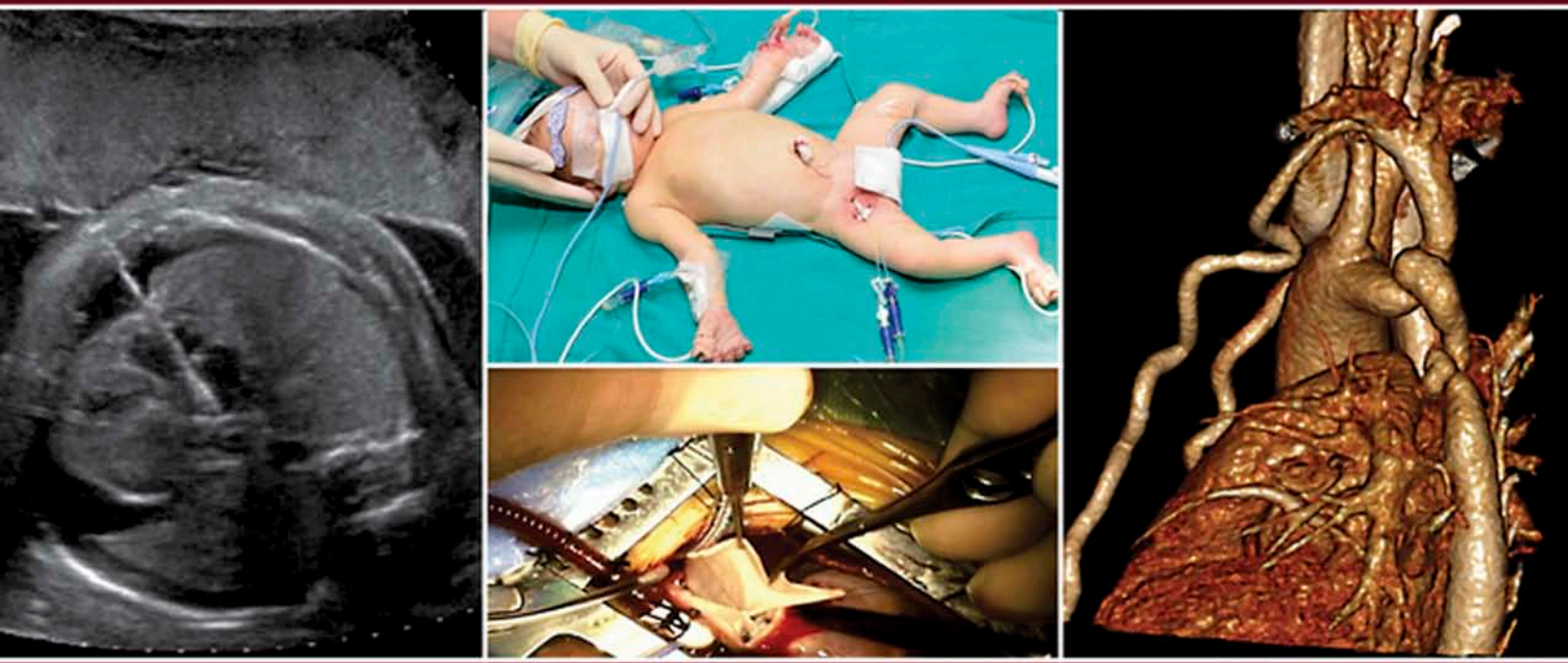
3rd Edition

ANESTHESIA FOR CONGENITAL HEART DISEASE



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Anesthesia for Congenital Heart Disease

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Cover design: From left to right: 1. (Left) Echocardiogram during fetal intervention for restrictive atrial septum in a fetus with hypoplastic left heart syndrome. Catheter with balloon can be visualized crossing atrial septum. Image courtesy of Shaine Morriss, M.D., Texas Children's Hospital. 2. (Top Center) Neonate with dextro transposition of the great arteries, after induction of anesthesia and placement of monitors and invasive catheters. Photo courtesy of Phillip Steffek, Texas Children's Hospital. 3. (Bottom Center) Surgical field during regional cerebral perfusion for aortic arch reconstruction for hypoplastic left heart syndrome. Aortic cannula is inserted into the distal end of a 3.5 mm polytetrafluoroethylene shunt anastomosed to the right innominate artery to provide cerebral blood flow. A bloodless surgical field is established by snaring brachiocephalic vessels and descending aorta. Photo courtesy Charles D. Fraser, MD, Texas Children's Hospital 4. (Right) Three-dimensional reconstruction of a computed tomographic angiogram of a 12 year old with untreated coarctation of the aorta. Severe coarctation of the aortic isthmus, presumably at the site of ductal insertion, located 2.1-cm distal to the takeoff of the left subclavian artery, with minimum caliber of 5.6 × 5.1 mm. Bilobed ductal aneurysm protruding ventrally at the site of the coarctation. Associated hypoplasia, tortuosity, and mild kinking of the distal transverse arch. Mild stenosis of the origin of the left subclavian artery with poststenotic dilation. Significant dilation of the mammary and intercostal arteries, which provide collateral blood flow to the body

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Preface

The third edition of *Anesthesia for Congenital Heart Disease* is a major update and expansion of the textbook that reflects the ongoing development of the practice of pediatric and congenital cardiac anesthesia, and the burgeoning knowledge base in this exciting field. All chapters have been thoroughly revised and updated with new sections and numerous recent references. Additional chapters have been included in two important areas of critical knowledge and practice, addressing anesthetic and sedative neurotoxicity in the patient with congenital heart disease (Chapter 9) and anesthesia in the patient with pulmonary hypertension (Chapter 28). Both of these chapters are written by true experts in these fields and are worthy of their own separate treatment. Also, for the first time, this edition of the textbook is in color, and numerous new illustrations and figures have been added to present a vibrant representation of cardiovascular anatomy and surgical approaches that are essential to the knowledge base for the congenital cardiac anesthesiologist. In addition, after each major section in every chapter, key learning points are presented to highlight important concepts and enhance knowledge retention. Each chapter is accompanied by five multiple-choice questions covering the most crucial learning points in each chapter, to optimize the learning experience for readers at all levels of training and clinical experience. These questions can be found in the on-line book supplement at http://www.wiley.com/go/andropoulos/congenitalheart.

We are pleased to welcome our Texas Children's Hospital colleague, Wanda C. Miller-Hance, MD, as Co-Editor of this text. Dr. Miller-Hance is a fully trained pediatric and congenital cardiac anesthesiologist, pediatric cardiologist, and recognized authority in intraoperative echocardiography for congenital heart surgery. Reflecting the international scope of anesthesia for congenital heart disease and the many outstanding practitioners all over the world, a number of new international authors have been added from Germany, the United Kingdom, Australia, France, Japan, and Canada.

Finally, caring for patients with congenital heart disease requires a team of dedicated professionals that include congenital cardiac anesthesiologists, congenital heart surgeons, pediatric and adult congenital cardiologists, cardiac intensivists, cardiac interventionalists and imaging specialists, nurses, perfusionists, respiratory therapists, technicians, child life and social workers, and interpreters, among many others. We greatly appreciate the passion and commitment of the people in these disciplines, without whom we could not do our work. Finally, the patient and family are the focus of the team, and their courage and goodwill in the face of serious and complex illness always amaze and inspire us. It is to our patients and their families that *Anesthesia for Congenital Heart Disease*, third edition, is dedicated, in the hope that the knowledge contained in these pages will contribute to better outcomes for them.

It is the purpose of this, our third edition of *Anesthesia for Congenital Heart Disease*, to contribute to the fund of knowledge in our field and to enhance the care of children with heart disease by individuals from various disciplines worldwide.

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List of Abbreviations

α_2M	α_2-macroglobulin
AA	aortic atresia
ABC	Aristotle Basic Complexity
ABO-C	ABO-compatible
ABO-I	ABO-incompatible
ACE	angiotensin-converting enzyme
ACGME	Accreditation Council for Graduate Medical Education
ACHD	adult congenital heart disease
ACT	activated clotting time
ACTH	adrenocorticotropic hormone
AEG	atrial electrogram
AI	aortic insufficiency
AICD	automatic internal cardiac defibrillator
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
Akt	protein kinase B
ALCAPA	anomalous left coronary artery arising from the pulmonary artery
ALI	acute lung injury
ANF	atrial natriuretic factor
ANH	Acute normovolemic hemodilution
APAF-1	apoptotic protease activating factor 1
APERP	accessory pathway effective refractory period
APOE	apolipoprotein E
APRV	airway pressure release ventilation
aPTT	activated partial thromboplastin time
APW	aortopulmonary window
AR	adrenergic receptor
ARCAPA	anomalous right coronary artery from the pulmonary artery
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
ASD	atrial septal defect
ASE	American Society of Echocardiography
ASO	arterial switch operation
AT	atrial tachycardia
ATIII	antithrombin III
ATP	adenosine triphosphate
AUC	area under the curve
AV	atrioventricular
AVC	atrioventricular canal
AVNRT	atrioventricular nodal re-entry tachycardia
AVSD	atrioventricular septal defect
BAV	bicuspid aortic valve
Bax	B-cell lymphoma-2-associated X protein
BCAS	The Boston Circulatory Arrest Study
BCL-2	B-cell lymphoma-2
BCL-xL	B-cell lymphoma-extra large
BCPC	bi-directional cavopulmonary connection
BDNF	Brain-derived neurotrophic factor
BiVAD	biventricular ventricular assist device
BNP	brain natriuretic peptide
BOS	bronchiolitis obliterans syndrome
BPA	branch pulmonary artery
BPD	bronchopulmonary dysplasia
BSA	body surface area
BSID	Bayley Scales of Infant Development
BUN	blood urea nitrogen
C3PO	Congenital Cardiac Catheterization Project on Outcomes
CABG	coronary artery bypass grafting
CALM	congenital atresia of the left main coronary artery
cAMP	cyclic adenosine monophosphate
CAV	coronary artery vasculopathy
CAVC	complete atrioventricular canal
CAVF	coronary arteriovenous fistula
CBF	cerebral blood flow
CBG	corticosteroid-binding globulin
CCA	common carotid artery
CCAN	Congenital Cardiac Anesthesia Network
CCAS	Congenital Cardiac Anesthesia Society
CCB	calcium channel blocker
CCTGA	congenitally corrected transposition of the great arteries
CF	cystic fibrosis
cGMP	cyclic guanosine monophosphate
CHARM	Catheterization for Congenital Heart Disease Adjustment for Risk Method
CHD	congenital heart disease
CHF	congestive heart failure
CICU	cardiac intensive care unit
CIED	cardiovascular implantable electronic device

CIRCI	critical illness-related corticosteroid insufficiency
CL	cardiolipin
CLAD	chronic lung allograft dysfunction
CMR	cardiac magnetic resonance
$CMRO_2$	cerebral metabolic rate for oxygen consumption
CMV	cytomegalovirus
CO	carbon monoxide
CO	cardiac output
CoA	coarctation of the aorta
COP	colloid osmotic pressure
COx	cerebral oximetry index
CPAP	continuous positive airway pressure
CPB	cardiopulmonary bypass
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRBSIs	catheter-related bloodstream infections
CRMDs	cardiac rhythm management devices
CSA	cross-sectional area
CSOR	cerebral–splanchnic oxygen ratio
CT	computed tomography
CUF	conventional ultrafiltration
CVC	central venous catheter
CVVH	continuous veno-venous hemofiltration
CVVH/D	continuous veno-venous hemofiltration and dialysis
dATP	deoxyadenosine triphosphate
DBD	donation after brain death
DCD	donation after cardiac death
DCM	dilated cardiomyopathy
DCRV	double-chambered right ventricle
DHCA	deep hypothermic circulatory arrest
DIC	diffuse intravascular coagulation
DIVA	difficult intravenous access
DLCO	diffusing capacity for carbon monoxide
DLT	double-lumen tube
DNA	deoxyribonucleic acid
DO_2	oxygen delivery
DORV	double outlet right ventricle
D-TGA	dextro-transposition of the great arteries
DVT	deep vein thrombosis
EA	Ebstein's anomaly
EACA	ε-aminocaproic acid
EACTS	European Association for Cardio-Thoracic Surgery
EAT	ectopic atrial tachycardia
EBV	estimated blood volume
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ECPR	extracorporeal cardiopulmonary resuscitation
ECPR	extracorporeal membrane oxygenation as part of cardiopulmonary resuscitation
EDA	end-diastolic area
EDV	end-diastolic volume
EEG	electroencephalogram
EF	ejection fraction
EFE	endocardial fibroelastosis
EJV	external jugular vein
ELSO	Extracorporeal Life Support Organization
EMA	European Medicines Agency
EMI	electromagnetic interference
EP	electrophysiological
EPDCs	epicardially derived cells
EPO	recombinant human erythropoietin alpha
ERA	endothelin receptor antagonist
ERK	extracellular signal-regulated protein kinase
ESA	end-systolic area
ESV	end-systolic volume
ET-1	endothelin-1
$EtCO_2$	end-tidal CO_2
ETT	endotracheal tube
FAC	fractional area change
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FHF	first heart field
FiO_2	fraction of inspired oxygen
FOB	fiberoptic bronchoscope
FRC	functional residual capacity
FTR	failure to resuscitate
FV	femoral vein
FVC	forced vital capacity
FVL	FV Leiden
GABA	γ-aminobutyric acid
GDP	guanosine diphosphate
GFR	glomerular filtration rate
GI	gastrointestinal
GLUTs	glucose transporters
Gp	glycoprotein
GSK-3β	glycogen synthase kinase-3β
GTP	guanosine triphosphate
HAT	heparin-associated thrombocytopenia
HCII	heparin cofactor II
Hct	hematocrit
HEAL	Health Education Assets Library
HFOV	high-frequency oscillatory ventilation
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigens
HLHS	hypoplastic left heart syndrome
HPA	hypothalamic–pituitary–adrenal axis
HPAH	heritable pulmonary artery hypertension
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
HTK	histidine-tryptophan-ketoglutarate
HUS	head ultrasound
IAA	interrupted aortic arch
IABP	intra-arterial blood pressure
IAS	interatrial septum
ICE	Intracardiac echocardiography
ICH	intracranial hemorrhage
ICU	intensive care unit
IE	infective endocarditis

IgG	immunoglobulin G
IJV	internal jugular vein
IM	intramuscular
iNO	inhaled nitric oxide
INR	international normalized ratio
IO	inflow occlusion
IPAH	idiopathic pulmonary artery hypertension
IPCCC	International Pediatric and Congenital Cardiac Code
ISHLT	Scientific Registry of the International Society for Heart and Lung Transplantation
IU	international unit
IV	intravenous
IVC	inferior vena cava
IVH	intraventricular hemorrhage
JCAHO	Joint Commission for the Accreditation of Hospital Organizations
JET	junctional ectopic tachycardia
KIM-1	kidney injury molecule-1
LA	left atrium
LAA	left aortic arch
LAA	left atrial appendage
LAP	left atrial pressure
LAS	lung allocation score
LBBB	left bundle branch block
LBW	low birth weight
LBWN	low-birth-weight neonate
LCOS	low cardiac output syndrome
LDLLT	living donor lobar lung transplant
LE	lower esophageal
L-FABP	liver fatty acid-binding protein
LiDCO	lithium dilution CO
LMA	laryngeal mask airway
LMWH	low-molecular-weight heparin
LPA	left pulmonary artery
LQTS	long QT syndrome
LSVC	persistent left superior vena cava
L-TGA	levo-transposition of the great arteries
LV	left ventricle, left ventricular
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
MAC	minimum alveolar concentration
MAP	mean arterial pressure
MAS	meconium aspiration syndrome
MAT	multifocal atrial tachycardia
mBTS	modified Blalock–Taussig shunt
MCS	mechanical circulatory support
MDI	Mental Development Index
MMF	mycophenolate mofetil
MOD	method of discs
MPA	main pulmonary artery
mPAP	mean pulmonary artery pressure
MPTP	mitochondrial permeability transition pore
MR	mitral regurgitation
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSOF	multisystem organ failure
mTOR	mammalian target of rapamycin
MUF	modified ultrafiltration
MV	mechanical ventilation
NAC	N-acetylcysteine
NEC	necrotizing enterocolitis
NGAL	neutrophil gelatinase-associated lipocalin
NICU	neonatal intensive care unit
NIRS	near-infrared spectroscopy
NMDA	*N*-methyl-D-aspartate
NOS	nitric oxide synthase
OB	obliterative bronchitis
OEF	oxygen excess factor
OER	oxygen extraction rate
OHT	orthotopic heart transplantation
OPTN	Organ Procurement and Transplant Network
OR	operating room
$p75^{NTR}$	p75 neurotrophic receptor
PA	pulmonary artery
PA	pulmonary atresia
PA/IVS	pulmonary atresia with intact ventricular septum
PAA	pharyngeal arch arteries
PAC	premature atrial contraction
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PAD	preoperative autologous donation
PAH	pulmonary artery hypertension
PAH-CHD	pulmonary artery hypertension associated with congenital heart disease
PAI	plasminogen activator inhibitor
PAO_2	alveolar oxygen tension
PaO_2	partial pressure of oxygen in arterial blood
PAPVC	partial anomalous pulmonary venous connection
PAPVD	partial anomalous pulmonary venous drainage
PAPVR	partial anomalous pulmonary venous return
PASP	pulmonary artery systolic pressure
PBF	pulmonary blood flow
PC	protein C
pCAS	pediatric cardiopulmonary assist system
PCC	prothrombin complex concentrate
PCWP	pulmonary capillary wedge pressure
PD	peritoneal dialysis
PDA	patent ductus arteriosus
PDC	peritoneal drainage catheter
PDE	phosphodiesterase
PDE-5	phosphodiesterase-5
PDEIs	phosphodiesterase inhibitors
PEEP	positive end-expiratory pressure
PEO	proepicardial organ
PF4	platelet factor 4
PFO	patent foramen ovale
PG	pressure gradient
PGE_1	prostaglandin E_1

PH	pulmonary hypertension
PHT	pulmonary hypertension
PI	pulmonary insufficiency
PICC	peripherally inserted central catheter
PIP	peak inspiratory measurement
PI-PLC	phosphatidylinositol-specific phospolipase C
PKA	protein kinase A
PKC	protein kinase C
PLC	phospolipase C
PMP	poly-(4-methyl-1-pentene)
POCA	Pediatric Perioperative Cardiac Arrest Registry
PPL	polypropylene
PPS	postpericardiotomy syndrome
PPV	positive pressure ventilation
PRA	panel reactive antibody
pRIFLE	pediatric modification of the RIFLE score
PRISM	Pediatric Risk of Mortality
PS	protein S
PS	pulmonary stenosis
PS/IVS	pulmonary stenosis with intact ventricular septum
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorder
PTT	partial thromboplastin time
PV	pulmonary valve
PVCs	premature ventricular contractions
PVD	pulmonary vascular disease
PVP	pulmonary valve perforation
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
Qp	pulmonary blood flow
Qs	systemic blood flow
RA	right atrium
RAA	right aortic arch
RACHS-1	Risk Adjustment for Congenital Heart Surgery
RAP	right atrial pressure
RBBB	right bundle branch block
RBC	red blood cell
RCP	regional cerebral perfusion
RDS	respiratory distress syndrome
rFVIIa	recombinant activated factor VIIa
RIFLE	risk, injury, failure, loss and end-stage renal disease
RIPC	remote ischemic preconditioning
ROS	reactive oxygen species
RPA	right pulmonary artery
RV	right ventricle, right ventricular
RVDCC	right ventricle-dependent coronary circulation
RVOT	right ventricular outflow tract
RVOTO	right ventricular outflow tract obstruction
RVSP	right ventricular systolic pressure
SAN	sinoatrial node
SaO_2	arterial oxygen saturation
SCA	Society of Cardiovascular Anesthesiologists
SCPA	superior cavopulmonary anastomosis
SCV	subclavian vein
$ScvO_2$	central venous oxygen saturation
SERCA	sarcoplasmic reticulum Ca^{2+}-ATPase
SF	shortening fraction
SGOT	serum glutamic oxaloacetic transaminase
SHF	second heart field
SIRS	systemic inflammatory response syndrome
$SjvO_2$	jugular bulb venous oximetry
SLV	single-lung ventilation
SPA	Society for Pediatric Anesthesia
SpO_2	pulse oximeter saturation
SR	sarcoplasmic reticulum
SSI	surgical site infection
STAT	Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery mortality score
STS	Society of Thoracic Surgeons
STS-CHSD	Society of Thoracic Surgeons Congenital Heart Surgery Database
subAS	subvalvular aortic stenosis
SV	stroke volume
SVAS	congenital supravalvular aortic stenosis
SVC	superior vena cava
SvO_2	percentage of oxygen saturation of mixed venous blood
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
SVT	supraventricular tachycardia
T3	triiodothyronine
T4	thyroxine
TA	tranexamic acid
TA	tricuspid atresia
TAFI	thrombin-activatable fibrinolysis inhibitor
TAPVC	total anomalous pulmonary venous connection
TAPVR	total anomalous pulmonary venous return
TCAD	transplant coronary artery disease
TDI	tissue Doppler imaging
TEE	transesophageal echocardiography
TEG	thromboelastography
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TGA	transposition of the great arteries
TGC	tight glycemic control
TI	tricuspid valve (TV) insufficiency
TLC	total lung capacity
TNF-alpha	tumor necrosis factor-alpha
TOF	tetralogy of Fallot
TOR	target of rapamycin protein
tPA	tissue plasminogen activator
TPTD	transpulmonary thermodilution
TR	tricuspid regurgitation
TRALI	transfusion-related acute lung injury
TTE	transthoracic echocardiography

TV	tricuspid valve
UFH	unfractionated heparin
UNOS	United Network for Organ Sharing
URI	upper respiratory tract infection
V/Q	ventilation/perfusion
VA	ventriculoarterial
VAA	volatile anesthetic agent
VAC	video-assisted cardioscopy
VAD	ventricular assist device
VATS	video-assisted thoracoscopic surgery
VF	ventricular fibrillation
VMI	visual-motor integration
VO_2	oxygen consumption
vPEO	venous proepicardial organ
VSD	ventricular septal defect
VT	ventricular tachycardia
VTI	velocity time integral
vWF	von Willebrand factor
WHO	World Health Organization
WMI	white matter injury
WS	Williams syndrome
WUS	Wake Up Safe Database

About the Companion Website

Anesthesia for Congenital Heart Disease: Companion Website

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MCQ questions to accompany each chapter

Full reference lists

CHAPTER 1

History of Anesthesia for Congenital Heart Disease

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Introduction

Over the last 70 years, pediatric cardiac anesthesia has developed as a subspecialty of pediatric anesthesia, or a subspecialty of cardiac anesthesia, depending on one's perspective. It is impossible to describe the evolution of pediatric cardiac anesthesia without constantly referring to developments in the surgical treatment of congenital heart disease (CHD) because of the great interdependency of the two fields. As pediatric anesthesia developed, surgical treatments of children with CHD began to be invented, starting with the simple surgical ligation of a patent ductus arteriosus (PDA), moving on to sophisticated, staged repair of complex intracardiac lesions in low-birth-weight neonates requiring cardiopulmonary bypass (CPB) and circulatory arrest and then on to the most recent complex biventricular repair. Practically every advance in the surgical treatment of CHD had to be accompanied by changes in anesthetic management to overcome the challenges that impeded successful surgical treatment or mitigated morbidity associated with surgical treatment.

This history will mostly be organized around the theme of how anesthesiologists met these new challenges using the anesthetic armamentarium that was available to them at the time. The second theme running through this story is the gradual change of interest and focus from events in the operating room (OR) to perioperative care in its broadest sense, including perioperative morbidity. The last theme is the progressive expansion in the age range of patients routinely presenting for anesthesia and surgery, from the 9-year-old undergoing the first PDA ligation in 1938 [1] to the first fetus to have an intervention for critical aortic stenosis *in utero*, as reported in *The New York Times* in 2002 [2], and, more recently, to the adult with CHD.

This story will be told working through the different time frames – the first years (1938–1954); CPB and early repair (1954–1970); deep hypothermic circulatory arrest (DHCA) and introduction of prostaglandin E_1 (PGE_1) for PDA (1970–1980); hypoplastic left heart syndrome (HLHS) (1980–1990); refinement and improvement in mortality/morbidity (1990–2000); introduction of extracorporeal membrane oxygenation (ECMO) and increased emphasis on interventional cardiology and imaging modalities (2000–2010); expansion to the fetus and adult with CHD (2011); and on to the present time.

The first years: 1938–1954

This period began with the ligation of the PDA and continued with palliative operations. The first successful operation for CHD occurred in August 1938 when Robert E. Gross ligated the PDA of a 9-year-old girl. The operation and the postoperative course were smooth, but because of the interest in the case, the child was kept in the hospital until the 13th day. In the report of the case, Gross mentions

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that the operation was done under cyclopropane anesthesia, and continues: "The chest was closed, the lung being re-expanded with positive pressure anesthesia just prior to placing the last stitch in the intercostal muscles."

A nurse using a "tight-fitting" mask gave the anesthetic. There was no intubation and, of course, no postoperative ventilation. The paper does not mention any particular pulmonary complications, so it cannot have been much different from the ordinary postoperative course of the day [1].

In 1952, Dr. Gross published a review of 525 PDA ligations where many, if not all, of the anesthetics were administered by the same nurse anesthetist, under surgical direction [3]. Here he states: "Formerly we employed cyclopropane anesthesia for these cases, but since about half of the fatalities seemed to have been attributable to cardiac arrest or irregularities under this anesthetic, we have now completely abandoned cyclopropane and employ ether and oxygen as a routine." It is probably correct that cyclopropane under these circumstances with insufficient airway control was more likely to cause cardiac arrhythmias than ether. An intralaryngeal airway was used, which also served "to facilitate suction removal of any secretions from the lower airway" (and, we may add, the stomach). Dr. Gross claims that the use of this airway reduced the incidence of postoperative pulmonary complications. Without having a modern, rigorous review of this series, it is hard to know what particular anesthetic challenges other than these were confronted by the anesthetist, but we may assume that intraoperative desaturation from the collapsed left lung, postoperative pulmonary complications, and occasional major blood loss from an uncontrolled, ruptured ductus arteriosus were high on the list.

The next operation to be introduced was billed as "corrective" for the child with cyanotic CHD and was the systemic to pulmonary artery (PA) shunt. The procedure was proposed by Helen Taussig as an "artificial ductus arteriosus" and was first performed by Albert Blalock at Johns Hopkins Hospital in 1944. In a very detailed paper, Drs. Blalock and Taussig described the first three patients to undergo the Blalock–Taussig shunt operation. Dr. Harmel anesthetized the first and third patients, using ether and oxygen in an open drop method for the first patient and cyclopropane through an endotracheal tube for the third patient. The second patient was given cyclopropane through an endotracheal tube by Dr. Lamont. Whether the first patient was intubated is unclear, but it is noted that in all three cases, positive pressure ventilation was used to reinflate the lung [4]. Interestingly, in this early kinder and gentler time, the surgical and pediatric authors reporting the Blalock–Taussig operation acknowledged by name the pediatricians and house officers who took such good care of the children postoperatively, but still did not acknowledge in their paper the contribution of the anesthesiologists Lamont and Harmel. Although intubation of infants was described by Gillespie as early as 1939, it is difficult to say when precisely intubations became routine [5].

Drs. Harmel and Lamont reported in 1946 on their anesthetic experience of 100 operations for congenital malformations of the heart "in which there is pulmonary artery stenosis or atresia." They reported 10 anesthetic-related deaths in the series, so it is certain that they encountered formidable anesthetic problems in these surgical procedures [6]. This is the first paper we know of published in the field of pediatric cardiac anesthesia.

In 1952, Damman and Muller reported a successful operation in which the main PA was reduced in size and a band was placed around the artery in a 6-month-old infant with a single ventricle (SV). They state that morphine and atropine were given preoperatively, but no further anesthetic agents are mentioned. At that time infants were assumed to be oblivious to pain, so we can only speculate on what was used beyond oxygen and restraint [7].

Over the next 20 years, many palliative operations for CHD were added and a number of papers appeared describing the procedures and the anesthetic management. In 1948 McQuiston described the anesthetic technique used at the Children's Memorial Hospital in Chicago [8]. This is an excellent paper for its time, but a number of the author's conclusions are erroneous, although they were the results of astute clinical observations and the knowledge at the time. The anesthetic technique for shunt operations (mostly Potts' anastomosis) is discussed in some detail, but is mostly of historical interest today. McQuiston explained that he had no experience of anesthetic management used in other centers, such as the pentothal–N_2O–curare used at Minnesota or the ether technique used at the Mayo Clinic. McQuiston used heavy premedication with morphine, pentobarbital and atropine, and/or scopolamine; this is emphasized because it was important "to render the child sleepy and not anxious." The effect of sedation with regard to a decrease in cyanosis (resulting in making the child look pinker) is noted by the authors. They also noted that children with severe pulmonic stenosis or atresia do not decrease their cyanosis "because of very little blood flow," and these children have the highest mortality.

McQuiston pointed out that body temperature control was an important factor in predicting mortality and advocated the use of moderate hypothermia (i.e., "refrigeration" with ice bags), because of a frequently seen syndrome of hyperthermia. McQuiston worked from the assumption that hyperthermia is a disease in itself, but did not explore the idea that the rise in central temperature might be a symptom of low cardiac output with peripheral vasoconstriction. Given what we now know about shunt physiology, it is interesting to speculate that this "disease" was caused by pulmonary hyperperfusion after the opening of what would now be considered as an excessively large shunt, stealing a large portion of systemic blood flow.

In 1950 Harris described the anesthetic technique used at Mount Zion Hospital in San Francisco. He emphasized the use of quite heavy premedication with morphine, atropine, and scopolamine. The "basal anesthetic agent" was Avertin (tribromoethanol). It was given rectally and supplemented with N_2O/O_2 and very low doses of curare.

Intubation was facilitated by cyclopropane. The FiO_2 was changed according to cyanosis; and bucking or attempts at respiration were thought to be due to stimulation of the hilus of the lung. This was treated with "cocainization" of the hilus [9].

In 1952 Dr. Robert M. Smith discussed the circulatory factors involved in the anesthetic management of patients with CHD. He pointed out the necessity of understanding the pathophysiology of the lesion and also "the expected effect of the operation upon this unnatural physiology." That is, he recognized that the operations are not curative. The anesthetic agents recommended were mostly ether following premedication.

While most of these previous papers had been about tetralogy of Fallot (TOF), Dr. Smith also described the anesthetic challenges of surgery for coarctation of the aorta, that was introduced by Dr. Gross in the U.S. and Dr. Craaford in Sweden simultaneously in the year 1945. He emphasized the hypertension following clamping of the aorta and warned against excessive bleeding in children operated on at older ages using ganglionic blocking agents. This bleeding was far beyond what anesthesiologists now see in patients operated on at younger ages, before development of substantial collateral arterial vessels [10].

The heart–lung machine: 1954–1970

From 1954 to 1970 the development of what was then called the "heart–lung machine" opened the heart to surgical repair of complex intracardiac congenital heart defects. At the time, the initial high morbidity of early CPB technology seen in adults was even worse in children, particularly smaller children weighing less than 10 kg. Anesthetic challenges multiplied rapidly in association with CPB, coupled with early attempts at complete intracardiac repair. The lung as well as the heart received a large share of the bypass-related injuries, leading to increased postoperative pulmonary complications. Brain injury began to be seen and was occasionally reported, in conjunction with CPB operations, particularly when extreme levels of hypothermia were used in an attempt to mitigate the morbidity seen in various organ systems after CPB.

In Kirklin's initial groundbreaking report of intracardiac surgery with the aid of a mechanical pump–oxygenator system at the Mayo Clinic, the only reference to anesthetic management was a brief remark that ether and oxygen were given [11]. In Lillehei's description of direct vision intracardiac surgery in humans using a simple, disposable artificial oxygenator, there was no mention of anesthetic management [12]. What strikes a "modern" cardiac anesthesiologist in these two reports is the high mortality: 50% in Kirklin's series and 14% in Lillehei's series. All of these patients were children with CHD ranging in age from 1 month to 11 years. Clearly, such mortality and the associated patient care expense would not be tolerated today.

At that time, pediatric anesthesia was performed with open drop ether administration and later with ether using different non-rebreathing systems. Most anesthetics were given by nurses under the supervision of the surgeon. The first physician anesthetist to be employed by a children's hospital was Robert M. Smith in Boston in 1946.

The anesthetic agent that came into widespread use after ether was cyclopropane; in most of the early textbooks, it was the recommended drug for pediatric anesthesia. Quite apart from being explosive, cyclopropane was difficult to use. It was obvious that CO_2 absorption was necessary with cyclopropane to avoid hypercarbia and acidosis, which might precipitate ventricular arrhythmias. However, administration with a Waters' absorber could be technically difficult, especially as tracheal intubation was considered dangerous to the child's "small, delicate airway."

In all the early reports, it is noted or implied that the patients were awake (more or less) and extubated at the end of the operation. In the description of the postoperative course, respiratory complications were frequent, in the form of either pulmonary respiratory insufficiency or airway obstruction. This latter problem was probably because "the largest tube which would fit through the larynx" was used. Another reason may have been that the red rubber tube was not tissue-tested. The former problem was probably often related to the morbidity of early bypass technology on the lung.

Arthur S. Keats, working at the Texas Heart Institute and Texas Children's Hospital with Denton A. Cooley, had much experience with congenital heart surgery and anesthesia from 1955 to 1960, and provided the most extensive description of the anesthetic techniques used in this era [13,14]. He described anesthesia for congenital heart surgery without bypass in 150 patients, the most common operations being PDA ligation, Potts' operation, atrial septectomy (Blalock–Hanlon operation), and pulmonary valvotomy. Premedication was with oral or rectal pentobarbital, chloral hydrate per rectum, intramuscular meperidine, and intramuscular scopolamine or atropine. Endotracheal intubation was utilized, and ventilation was assisted using an Ayres T-piece, to-and-fro absorption system, or a circle system. Cyclopropane was used for induction, and a venous cutdown provided vascular access. Succinylcholine bolus and infusion were used to maintain muscle relaxation. Light ether anesthesia was used for maintenance until the start of chest closure, and then 50% N_2O was used as needed during chest closure. Of note is the fact that the electrocardiogram (ECG), ear oximeter, and intra-arterial blood pressure (IABP) recordings were used for monitoring during this period, as well as arterial blood gases and measurements of electrolytes and hemoglobin. The following year he published his experiences with 200 patients undergoing surgery for CHD with CPB, almost all of whom were children. Ventricular septal defect (VSD), atrial septal defect (ASD), TOF, and aortic stenosis were the most common indications for surgery. The anesthetic techniques were

the same as described earlier, except that d-tubocurare was given to maintain apnea during the bypass. In 1957, in addition to ECG, IABP, and oximeter, Dr. Digby Leigh noted the importance of capnography in cardiac surgery. He described the effect of pulmonary blood flow on end-tidal CO_2 ($EtCO_2$) and the decrease in $EtCO_2$ after partial clamping of the PA during the Blalock–Taussig shunt procedure. However, it was not until 1995 that Smolinsky et al. reported the importance of $EtCO_2$ during PA banding [15–17].

Perfusion rates of 40–50 mL/kg/min were used in infants and children, and lactic acidemia after bypass (average 4 mmol/L) was described. No anesthetic agent was added during the bypass procedure, and "patients tended to awaken during the period of bypass," but apparently without recall or awareness. Arrhythmias noted ranged from frequent bradycardia with cyclopropane and succinylcholine to junctional or ventricular tachycardia, ventricular fibrillation (VF), heart block, and rapid atrial arrhythmias. Treatments included defibrillation, procainamide, digitalis, phenylephrine, ephedrine, isoproterenol, and atropine. Eleven out of 102 patients with VSD experienced atrioventricular block. Epicardial pacing was attempted in some of these patients but was never successful. Fresh citrated whole blood was used for small children throughout the case, and the transfusion of large amounts of blood was frequently necessary in small infants. The mortality rate was 13% in the first series (36% in the 42 patients less than 1 year old) and 22.5% in the second series (47.5% in the 40 patients less than 1 year old). Causes of death included low cardiac output after ventriculotomy, irreversible VF, coronary air emboli, postoperative atrioventricular block, hemorrhage, pulmonary hypertension, diffuse atelectasis, and aspiration of vomitus. No death was attributed to the anesthetic alone. Reading these reports provides an appreciation of the daunting task of giving anesthesia during these pioneering times.

Tracheostomy after cardiac operations was not unusual and in some centers was done "prophylactically" a week before the scheduled operation. These practices were certainly related to primitive (relative to the present) techniques and equipment used for both endotracheal intubation and CPB. Postoperative ventilatory support did not become routine until later when neonatologists and other intensive care specialists had proved it could be done successfully. Successful management of prolonged respiratory support was first demonstrated in the great poliomyelitis epidemics in Europe and the USA in 1952–1954 [18].

Halothane was introduced in clinical practice in the mid-1950s and it rapidly became the most popular agent in pediatric anesthesia, mostly because of the smooth induction compared with the older agents. Halothane was also widely used for pediatric cardiac anesthesia in spite of its depressive effect on the myocardium and the significant risk of arrhythmias. Halothane is no longer available, and the newer inhalational agents, isoflurane and sevoflurane, are now the mainstays of pediatric cardiac cases in US academic centers.

During this period, adult cardiac anesthesiologists, following the practice reported by Edward Lowenstein in 1970 [19], began to use intravenous anesthesia based on opiates. Initially, morphine in doses up to 1 mg/kg was given with 100% oxygen and this technique became the anesthetic of choice for adult cardiac patients, but vasodilation and hypotension associated with its use slowed the incorporation of this technique into pediatric cardiac anesthesia until the synthetic opiates became available.

Before CPB was developed, or when it still carried high morbidity and mortality, a number of modalities were used to improve the outcome for infants. One was inflow occlusion (IO) and another was the hyperbaric chamber. IO was useful and, if well managed, an elegant technique. The secret was the organization of the efforts of the entire operative team, and the technique required the closest cooperation between surgeons and anesthesiologists. The technique was as follows.

The chest was opened in the midline. After pericardiotomy, a side clamp was placed on the right atrial (RA) free wall and an incision made in the RA, or proximal on the PA, prior to placing the vascular clamps used to occlude caval return. Before application of the clamps, patients were hyperventilated with 100% O_2. During IO, the superior vena cava (SVC) and inferior vena cava (IVC) inflow were occluded, ventilation held, and the RA or PA clamp released; the heart was allowed to empty and the septum primum was excised or the pulmonic valve dilated. After excision of the septum or valvotomy, one caval clamp was released initially to de-air the atrium. The RA side clamp or the PA clamp was then reapplied and the other caval clamp released. The heart was resuscitated with bolus calcium gluconate (range 30–150 mg/kg) and bicarbonate (range 0.3–3 mEq/kg). Occasionally, inotropes were administered, most often dopamine. It was important to titrate the inotropes so as not to aggravate rebound hypertension caused by endogenous catecholamines. The duration of the IO was between 1 and 3 minutes – terrifying minutes for the anesthesiologist, but quickly over.

Another modality used to improve the survival after shunt operations, PA banding, and atrial septectomy was to operate in the hyperbaric chamber, thereby benefiting from the increased amount of physically dissolved oxygen. It was a cumbersome affair operating in crowded and closed quarters. There was room for only two surgeons, two nurses, one anesthesiologist, and one baby, as the number of emergency oxygen units limited access. Retired navy divers ran the chamber and kept track of how many minutes the personnel had been in the hyperbaric chamber in the previous week. Help was not readily available because the chamber was buried in a sub-basement and people had to be sluiced in through a side arm that could be pressurized. The chamber was pressurized to 2–3 atmospheres so it was unpleasantly hot while increasing the O_2 pressure and cold while decreasing the pressure;

people with glasses were at a disadvantage. It did not seem to add to survival and was abandoned around 1974.

Anesthesia was a challenge in the hyperbaric chamber. The infants were anesthetized with ketamine and nitrous oxide. As the pressure in the chamber increased, the concentrations of N_2O had to be decreased to avoid the hypotension and bradycardia that occurred rapidly.

Also in this era, the first infant cardiac transplant was performed by Kantrowitz in 1967 [20]. The recipient was an 18-day-old, 2.6 kg patient with severe Ebstein's anomaly, who had undergone a Potts' shunt on day 3 of life. The donor was an anencephalic newborn. The anesthetic technique is not described, and the infant died of pulmonary dysfunction 7 hours postoperatively.

The era of deep hypothermic circulatory arrest and the introduction of PGE_1: 1970–1980

Sometime around 1970 physiological repair of CHD, or "correction," had begun to come of age. In the adult world, coronary bypass operations and valve replacement spurred interest in cardiac anesthesia, which centered increasingly on use of high-dose narcotics and other pharmacological interventions. As synthetic opiates with fewer hypotensive side-effects became available, their use spread into pediatric cardiac anesthesia in the late 1970s and 1980s.

Children were still treated as "small adults" because major physiological differences were not yet well appreciated, particularly as they related to CPB morbidity. CPB was rarely employed during surgery on children weighing less than 9 kg because of the very high mortality and morbidity that had been experienced in the early years. The notion of repairing complex CHD in infancy was getting attention but was hindered by technical limitations of surgical techniques, CPB techniques, and anesthetic challenges in infants. Theoretically, physiological repair early in life provides a more normal development of the cardiovascular and pulmonary systems and might avoid palliation altogether. The advantage of this was that the sequelae after palliation, for instance distorted pulmonary arteries after shunts and PA banding, might be avoided. Pulmonary artery hypertension following Waterston and Potts' shunts occurred as a result of increased pulmonary blood flow and resulted in pulmonary vascular obstructive disease. This would not develop if the defect were physiologically repaired at an early age. Furthermore, parents could be spared the anxiety of repeated operations and the difficulties of trying to raise a child with a heart that continued to be impaired.

The perceived need for early repair, together with the high mortality of bypass procedures, in infants and small children led to the introduction of DHCA. It was first practiced in Kyoto, Japan, but spread rapidly to Russia, the west coast of the US at Seattle, Washington, and from there to Midwestern and other US pediatric centers. One example of the difficulties this presented to anesthesiologists was the introduction of DHCA in practice at Boston Children's Hospital. The newly appointed chief of cardiovascular surgery at the Boston Children's Hospital was Aldo R. Castaneda, MD, PhD, one of the first supporters of early total correction of CHD, who quickly embraced DHCA as a tool to accomplish his goals for repair in infants. In 1972, he immediately introduced DHCA into practice at Boston Children's Hospital and the rather shocked anesthesia department had to devise an anesthetic technique to meet this challenge, aided only by a couple of surgical papers in Japanese that Dr. Castaneda kindly supplied. Of course, these papers made little reference to anesthesia.

The first description of the techniques of DHCA from Japan in the English literature was by Horiuchi in 1963 [21]. This involved a simple technique with surface cooling and rewarming during resuscitation, using ether as the anesthetic agent, without intubation. In 1972 Mori et al. reported details of a technique for cardiac surgery in neonates and infants using deep hypothermia, again in a surgical publication [22]. Their anesthetic technique was halothane/N_2O combined with muscle relaxant; CO_2 was added to the anesthetic gas during cooling and rewarming (pH-stat) to improve brain blood flow. The infants were surface-cooled with ice bags and rewarmed on CPB.

Surprisingly, given the enormity of the physiological disturbances and challenges presented by DHCA, very few articles describing an anesthetic technique for DHCA were published, perhaps because DHCA and early correction were not widely accepted. A paper from Toronto described an anesthetic regime with atropine premedication occasionally combined with morphine [23]. Halothane and 50% N_2O were used, combined with d-tubocurare or pancuronium. CO_2 was added to "improve tissue oxygenation by maintaining peripheral and cerebral perfusion." The infants were cooled with surface cooling (plastic bags with melting ice) and rewarmed on CPB. It was noted that six of the 25 infants had VF when cooled to below 30 °C.

Given the lack of any scientific data or studies to guide anesthetic management of such cases, a very simple technique with ketamine–O_2–N_2O and curare supplemented by small amounts of morphine (0.1–0.3 mg/kg) was used at Boston Children's Hospital. This was the way in which infants were anesthetized for palliative cardiac surgical procedures in the hyperbaric chamber at Boston Children's Hospital. The infants were surface-cooled in a bathtub filled with ice water to a core temperature of approximately 30 °C. The bathtub consisted of a green plastic bucket (for dishwashing) bought at a Sears-Roebuck surplus store, keeping things as simple as possible (Figure 1.1). This method was used in hundreds of infants over the next couple of years and only one infant developed VF in the ice water bathtub. This was an infant with TOF who suffered a coronary air embolus either from a peripheral IV or during an attempted placement of a central venous line. In retrospect, it is amazing that so few

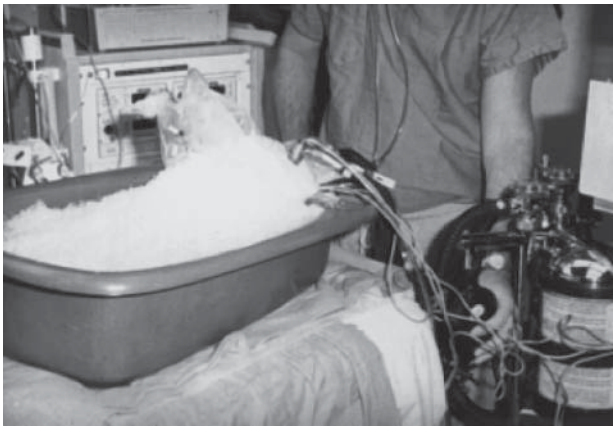

Figure 1.1 Infant submerged in ice water.

papers were published about the anesthetic management of this procedure, which was rapidly seen to be life-saving. The material that was published about these techniques was restricted to surgical journals and did not describe or make any attempt to study the anesthetic techniques used for DHCA. The published surgical articles were largely unknown to cardiac and pediatric anesthesiologists.

It was during this decade that the "team concept" developed, with cardiologists, cardiac surgeons, and anesthesiologists working together in the OR and the intensive care unit (ICU) in the larger centers. These teams were facilitated by the anesthesiologists' "invasion" of weekly cardiology–cardiac surgeons' conferences where the scheduled operations for the week were discussed. Dr. Castaneda, chief surgeon at Boston's Children's Hospital, was a leader in the creation of the cardiac team concept for pediatric cardiac surgery.

During the first year of using DHCA in Boston, it was noticed that a number of the infants had "funny, jerky" movements of the face and tongue. A few also had transient seizures during the postoperative period, but as they had normal electroencephalograms (EEGs) at 1-year follow-up, it was felt that significant cerebral complications were not a problem. In view of the knowledge developed subsequently, these clues to neurological damage occurring during and after pediatric cardiac surgery involving DHCA were overlooked. In hindsight, it is perhaps more accurate to say these clues were ignored, and as a result a great opportunity to study this problem was delayed for almost two decades. The issue of neurological damage with DHCA was raised repeatedly by surgeons such as John Kirklin, but was not really studied until the group at Boston Children's Hospital led by Jane Newburger and Richard Jonas systematically followed a cohort of infants who had the arterial switch operation in the late 1980s using DHCA techniques [24]. In the late 1980s and early 1990s, Greeley and co-workers at Duke performed a series of human studies delineating the neurophysiological response to deep hypothermia and circulatory arrest [25]. These studies provided the crucial data in patients from which strategies for cooling and rewarming, length of safe DHCA, blood gas management, and perfusion were devised to maximize cerebral protection.

Those ongoing studies were followed by a number of other studies comparing DHCA with hypothermic low-flow perfusion, with different hematocrit in the perfusate and with different pH strategies during hypothermic CPB, pH-stat versus alpha-stat.

During those years, the ketamine-morphine anesthetic technique had been supplanted by fentanyl-based high-dose narcotic techniques. For the neurological outcome studies, the anesthetic technique was very tightly controlled, using fentanyl doses of 25 μg/kg at induction, incision, onset of bypass and on rewarming, in addition to pancuronium. From the beginning of this period, surgical results as measured by mortality alone were excellent, with steady increases in raw survival statistics. Because anesthetic techniques were evolving over this period of time, it was difficult to definitely ascribe any outcome differences to different anesthetic agents. A 1984 study of 500 consecutive cases of cardiac surgery in infants and children looked at anesthetic mortality and morbidity. Both were very low – so low in fact that they were probably not universally believed [26].

As the new synthetic opioids such as fentanyl and sufentanil were developed, they replaced morphine to provide more hemodynamic stability in opiate-based anesthetic techniques for cardiac patients. In 1981 Gregory and his associates first described the use of "high-dose" fentanyl 30–50 μg/kg combined with pancuronium in 10 infants undergoing PDA ligation. It is noteworthy that transcutaneous oxygen tension was measured as part of this study. This paper was, in fact, the introduction of high-dose narcotics in pediatric cardiac anesthesia [27]. The technique was a great success; one potential reason for this was demonstrated 10 years later in Anand's paper showing attenuation of stress responses in infants undergoing PDA ligation who were given lesser doses of fentanyl in a randomized, controlled study [28].

During this same period, synthetic opioids were replacing morphine in adult cardiac surgery. This technique slowly and somewhat reluctantly made its way into pediatric anesthesia [29], replacing halothane and morphine, which had previously been the predominant choice of pediatric anesthesiologists dealing with patients with CHD. In the years from 1983 to 1995, a number of papers were published showing the effect of different anesthetic agents on the cardiovascular system in children with CHD. Ketamine, nitrous oxide, fentanyl, and sufentanil were systematically studied. Some misconceptions stemming from studies of adult patients were corrected, such as the notion that N_2O combined with ketamine raises PA pressure and pulmonary vascular resistance (PVR) [30]. On the other hand, the role of increased $PaCO_2$ or lower pH in causing higher PVR was also demonstrated and that subsequently became important in another connection [31]. A number of studies done at this time demonstrated in a controlled fashion the earlier clinical observation (Harmel and McQuiston in the late 1940s) [6,32] that in

cyanotic patients the O_2 saturation would rise during induction of anesthesia, almost irrespective of the agent used [33]. These events only serve to reinforce the value of acute clinical observation and provide an example of how the interpretation of such observations may well change as new knowledge is discovered.

PDA and the introduction of PGE_1

In the mid-1970s, several discoveries were made and introduced into clinical practice that turned out to be of great importance to the pediatric cardiac anesthesiologist and the rest of the cardiac team, the most important being the discovery that PGE_1 infused intravenously prevented the normal ductal closure [34]. These developments revolved around the role of the PDA in the pathophysiology of both cyanotic and acyanotic CHD. The critical role of PDA closing and opening in allowing early neonatal survival of infants with critical CHD began to be appreciated and clinicians sought methods of either keeping the PDA open or closing it, depending on what type of critical CHD the neonate was born with and the role of patency of the ductus arteriosus in the CHD pathophysiology. In some cases, particularly in very small neonates, the importance of closing the PDA was increasingly appreciated and, in other cases, the critical importance of maintaining the patency of a PDA was appreciated.

As the survival of very small premature infants ("preemies") began to improve, mostly because of technical improvements with the use of a warmed isolette and improved mechanical ventilation, it became apparent that in many of these infants the PDA would not undergo the normal closure over time. As the understanding of these infants' physiological problems improved and more infants survived, the role of continued patency of the PDA in neonates needing mechanical ventilation was appreciated. This led to medical therapy directed at promoting ductal closure using aspirin and indomethacin.

When such attempts failed, it was increasingly understood that necrotizing enterocolitis in the preemie was associated with decreased mesenteric blood flow secondary to the "steal" of systemic blood flow into the pulmonary circulation through a PDA. Thus, in cases when the PDA failed to close in premature infants, the need for operative treatment of the PDA in preemies arose as prophylaxis for necrotizing enterocolitis.

Pediatric and cardiac anesthesiologists were now faced with the task of anesthetizing these tiny preemies safely. This involved maintaining body temperature in infants of 1 kg or less with very large surface area/volume ratios. Intraoperative fluid restriction was important and low levels of FiO_2 were used to decrease the risk of retinopathy of prematurity. As the decade progressed, these issues emerged and were addressed. In 1980, Neuman [35] described the anesthetic management of 70 such infants using an O_2/N_2O muscle relaxant anesthesia technique with no mortality. Low FiO_2 was used to reduce the risk of retrolental fibroplasia and precautions were taken to prevent heat loss. In those days before human immunodeficiency virus (HIV) became a wide concern, 40% of the infants received blood transfusion. Interestingly, the question of whether to operate in the neonatal intensive care unit (NICU) or the OR for closure of the PDA in the preemie was debated at that time and remains unsettled today.

The PDA lesion presents an interesting story. In 1938 it was the first of the CHD lesions to be successfully treated surgically [1]. In the mid-1970s it was closed with medical therapy, first with aspirin and later with indomethacin. It was the first CHD lesion to be treated in the catheterization laboratory using different umbrella devices or coils [36]. Presently, if surgical closure is necessary, it is often done using a minimally invasive, thoracoscopic video-assisted technique [37]. Thoracoscopy has the benefit of using four tiny incisions to insert the instruments, avoiding an open thoracotomy and limiting dissection and trauma to the left lung. At the same time, this latest development of surgical technique required the anesthesiologist once again to change the anesthetic approach to these patients. Unlike adult anesthesiologists, who can use double-lumen endotracheal tubes for thoracoscopic procedures, pediatric anesthesiologists caring for 1–3 kg infants undergoing PDA ligation do not have the luxury of managing the left lung [37]. Another problem posed by thoracoscopic PDA ligation in the infant is the emerging need for neurophysiological monitoring of the recurrent laryngeal nerve's innervation of the muscles of the larynx to avoid injury, a known complication of PDA surgery [38]. The last issue is tailoring the anesthetic so that the children are awake at the end of the operation, extubated, and spend an hour or so in the post-anesthesia care unit, bypassing the cardiac ICU. In fact, in 2001, a group led by Hammer at Stanford published the first description of true outpatient PDA ligation in two infants aged 17 days and 8 months [39]. These patients were managed with epidural analgesia, extubated in the OR, and discharged home 10 hours postoperatively. This report brings PDA closure full circle from a 13-day hospital stay following an ether mask anesthetic for an open thoracotomy to a day surgery procedure in an infant undergoing an endotracheal anesthetic for a thoracoscopic PDA ligation.

Maintaining patency of the PDA using PGE_1 is probably now of considerably greater importance than its closure both numerically and in terms of being life-sustaining in neonates with critical CHD. The introduction of PGE_1 suddenly improved the survival rate of a large number of neonates, with CHD having ductal-dependent lesions to improve pulmonary blood flow, or to improve systemic blood flow distal to a critical coarctation of the aorta. The introduction of PGE_1 into clinical practice for therapy of neonatal CHD substantially changed the lives of pediatric cardiac surgeons and anesthesiologists, as frequent middle-of-the-night shunt operations with extremely cyanotic infants almost immediately became a thing of the past. These operations were particularly daunting when one realizes that these procedures were most common before the availability of pulse oximetry; the only warning

signs of impending cardiovascular collapse were the very dark color of the blood and preterminal bradycardia. To get an arterial blood gas with a PaO_2 in the low teens was not uncommon and PaO_2 measurements in single digits in arterial blood samples from live neonates during such surgical procedures were recorded. Even more dramatic was the disappearance of the child with critical post-ductal coarctation. These infants were extremely acidotic, with a pH of 7.0 or less at the start of the procedure (if it was possible to obtain an arterial puncture); they looked mottled and almost dead below the nipples. With the advent of PGE_1 therapy, they were resuscitated medically in the ICU and could be operated on the following day in substantially better condition than was previously the case.

But the introduction of PGE_1 had an effect that was not clearly foreseen except possibly by some astute cardiologists. Survival of a number of these neonates presented pediatric cardiologists and cardiac surgeons (and then anesthesiologists) with rare and severe forms of CHD that had hitherto been considered a "rare" pathological diagnosis. Foremost among these were the infants with HLHS and some forms of interrupted aortic arch. As further experience was gained, it became obvious that these forms of disease were not so rare, but infants who had survived with those forms of CHD were very rare.

The story of HLHS: 1980–1990

As mentioned in the previous section, the introduction of PGE_1 brought major changes to pediatric cardiac anesthesia, solving some problems and at the same time bringing new challenges for the cardiac team. New diagnoses of CHD presented for treatment and were recognized; some had been known previously but had until then presented insurmountable obstacles to any effective therapy.

One of these was HLHS. It had been accurately described in 1958 by Noonan and Nadas but only as a pathological diagnosis [40]. The syndrome is a ductus lesion, with 100% mortality within a few days to weeks when the ductus underwent physiological closure. HLHS was therefore of no practical interest from a therapeutic standpoint until ductal patency could be maintained. When it became possible to keep the ductus arteriosus patent with PGE_1, these neonates rapidly became a problem that could not easily be ignored. In the beginning, most of the infants were misdiagnosed as having sepsis and being in septic shock, and few babies reached the tertiary center without a telltale Band-Aid, indicating a lumbar puncture to rule out sepsis.

But even with the ability to diagnose the defect in a live neonate temporarily kept alive with a PGE_1 infusion, the outlook was not much better. There was no operation devised, and in some centers such neonates were kept viable on a PGE_1 infusion for weeks and even months in the (usually) vain attempt to get them to grow large enough for some surgical procedure to be attempted. In subsequent years, several centers tried different approaches with ingenious conduits, attempting to create an outlet from the right ventricle to the aorta and the systemic circulation.

Those were also the years during which President Ronald Reagan's Baby Doe regulations were in effect. Anyone who thought an infant was being mistreated (i.e., not operated upon) could call a "hotline number" which was posted in all neonatal ICUs to report the physicians' "mistreatment" of the infant. Fortunately, these regulations died a quiet death after a few chaotic years [41].

In the meantime, the search for a palliative operation went on, also spurred by the increasing success of the Fontan operation, which had been introduced in 1970 [42]. This meant that there now was a theoretical endpoint for HLHS as well as for other forms of SV physiology. It was William Norwood at Boston Children's Hospital who was the first person to devise a viable palliation and also to complete the repair with a Fontan operation the following year [43]. The publication of this landmark paper spurred considerable discussion. Many cardiologists and surgeons took the position that this operative procedure represented experimental and unethical surgery and that these infants "were better off dead."

The current approach to these infants varies from multistage physiological repair with palliation followed by Fontan operation. Another alternative is neonatal transplantation as proposed by the group at Loma Linda in California [44]. Some cardiologists are still advocates of conservative "comfort care" for neonates with HLHS. With eventual survival of about 70% being achieved in many centers, these infants can no longer be written off as untreatable. Now the question is more about quality of survival, especially intellectual development. It is also recognized that many have both chromosomal and non-chromosomal anomalies that affect the cerebral and gastrointestinal systems [45].

As was the case from the beginnings of pediatric cardiac surgery, this new patient population presented a management dilemma for the anesthesiologists; they posed a new set of problems that required a solution before acceptable operative results could be achieved. It was obvious that patients with HLHS were hemodynamically unstable before CPB because of the large volume load on the heart coupled with coronary artery supply insufficiency. The coronary arteries in HLHS are supplied from the PDA retrograde through a hypoplastic ascending and transverse aorta that terminates as a single "main" coronary artery. A common event at sternotomy and exposure of the heart was VF secondary to mechanical stimulation. This fibrillation was sometimes intractable, necessitating emergent CPB during internal cardiac massage. This was not an auspicious beginning to a major experimental open heart procedure.

It was during these years that there was a transition from morphine–halothane–N_2O to a high-dose narcotic technique with fentanyl or sufentanil combined with 100%

oxygen. This technique seemed to provide some protection against the sudden VF events compared with historical controls [46]. Despite this modest progress in getting patients successfully onto CPB, it soon became painfully clear that not much progress was made in treating this lesion when trying to wean the patients from bypass. The infants were still unstable coming off bypass and severely hypoxemic, and it took some time before we discovered a way to deal with the problem.

A chance observation led to a solution. Infants who came off bypass with low PaO_2 (around 30 mmHg) after the HLHS repair often did well, while the ones with immediate "excellent gases" ($PaO_2 \geq 40–50$ mmHg) became progressively unstable in the ICU a couple of hours later, developing severe metabolic acidosis and dying during the first 24 hours. This observation, combined with discussions with the cardiologists about PVR and systemic vascular resistance (SVR), led to attempts to influence these resistances to assure adequate systemic flow. In retrospect, infants with low PaO_2 after bypass had smaller aortopulmonary shunts and adequate systemic blood flow, while those with larger shunts and higher initial PaO_2 levels after weaning from bypass tended to "steal" systemic blood flow through the shunt. This would occur in the postoperative period, as the PVR remained elevated as a result of CPB before returning to more normal levels. These observations led to the technique of lowering the FiO_2 (sometimes as low as 0.21) and allowing hypoventilation to increase PVR in patients who had larger shunts placed to supply adequate systemic blood flow as part of what became known as the Norwood operation [46]. A different technique used at other institutions to deal with this problem was to add CO_2 to the anesthetic gas flow, increasing PVR and continuing to use "normal ventilation" in children who had larger shunts placed and excessive pulmonary blood flow [47]. Both techniques represented different approaches to the same problem: finding ways to deal with the need to carefully balance PVR and SVR after bypass in a fragile parallel circulation in the post-bypass period where dynamic changes were taking place in ventricular function.

These observations, and the subsequent modifications in anesthetic and postoperative management, improved the survival for the stage I palliation (Norwood procedure). It should be noted that the pediatric cardiac anesthesiologist was a full, contributing partner in the progressive improvement in outcome of this very complex and challenging lesion. More importantly, the techniques developed and the knowledge gained in this process also simplified the management of other patients with parallel circulation and SV physiology. The obvious example is truncus arteriosus, where the "usual" ST segment depression and frequent VF that occurred intraoperatively can almost always be avoided. Any decrease in PVR during anesthesia in a child with unrepaired truncus arteriosus can lead to pulmonary "steal" of systemic blood flow and decreased diastolic pressure through the common trunk to the aorta and PA, resulting in hypotension and insufficient systemic blood flow expressed initially as coronary insufficiency and ST depression (or elevation).

During the same decade, the surgical treatment of transposition of the great arteries (TGA) underwent several changes. The Mustard operations (as one type of atrial switch procedure) were feared because of the risk of SVC obstruction as a complication of this surgical procedure. At the end of a Mustard procedure, it was not uncommon to see a child with a grotesquely swollen head having to be taken back to the OR for immediate reoperation. Many of those children suffered brain damage, especially when reoperation was delayed. This resulted from low cerebral perfusion pressure during bypass because of venous hypertension in the internal jugular veins and SVC. The extent and prevalence of such damage were never systematically studied. The arterial pressure during bypass and in the immediate post-bypass period in the OR tended to be low and the pressure in the SVC high. An article from Great Ormond Street in London demonstrated arrested hydrocephalus in Mustard patients [48]. The Senning operation (another variant of the atrial switch approach to TGA) was better, but those children could develop pulmonary venous obstruction acutely in the OR, after the procedure or progressively after hospital discharge. When the diagnosis was not promptly made and acted upon, these infants were often quite sick by the time they came to reoperation.

The successful application of the arterial switch procedure described by Jatene then began to revolutionize operations for TGA [49]. It eliminated the risk of obstruction of the pulmonary and systemic venous return seen after the Mustard and Senning procedures. It also diminished the incidence of the subsequent sick sinus syndrome, a complication that might develop in the first 10 years postoperatively as a result of the extensive atrial suture lines and reconstructions required by these "atrial" switch procedures. The introduction of the arterial switch operation again involved anesthesiologists. The initial attempts at arterial switch operations in many institutions resulted in substantial numbers of infants who had severe myocardial ischemia and even frank infarcts. This was due to a variety of problems with the coronary artery transfer and reimplantation into the "switched" aorta that had been moved to the left ventricle outflow tract. Pediatric cardiac anesthesiologists gained extensive experience with intraoperative pressor and inotropic support and nitroglycerine infusions. They were expected by surgeons to provide support to get infants through what later turned out to be iatrogenically caused myocardial ischemia. As surgeons learned to handle coronary artery transfers and reanastomoses well, these problems largely disappeared, along with the need for major pressor and inotropic support and for nitroglycerine infusion inappropriately directed at major mechanical obstructions in the coronary arterial supply. The arterial switch operation has now been refined at most centers to the point where it is largely a "routine" procedure and it presents, for the most part, no unique anesthetic challenges.

It was during the same time period that a randomized strictly controlled study of stress response in infants undergoing cardiac surgery while anesthetized with high-dose sufentanil was performed. It showed that a high-dose narcotic technique would suppress but not abolish stress responses. It also seemed to show a reduction in morbidity and possibly mortality [50]. However, when the study was refined 10 years later using only high-dose narcotic anesthesia in various techniques, no mortality differences were seen between the various high-dose narcotic techniques. It must be pointed out that the patient population was older and the bypass technique had undergone some refinement [51].

Fontan and the catheterization laboratory: 1990–2000

After the anesthetic technique and preoperative management of the stage I palliation for HLHS had been refined and we had been encouraged by the initial successes of stage II, problems arose. The Fontan operation became problematic as it was applied to younger patients with a great variety of SV types of CHD. Many of the patients had seemingly perfect Fontan operations, but in the cardiac ICU they developed low cardiac output and massive pleural and pericardial effusions postoperatively. Many died in the postoperative period despite a variety of different support therapies; their course over the first 24–48 hours was relentlessly downward and could only be reversed by taking them back to the OR, reversing the Fontan operation and reconstructing a systemic to PA shunt. It was hard for the caretakers of these infants to accept such losses of children they had known from birth. They were our little friends and we knew the families too. All kinds of maneuvers were tried to avoid this sequence of events, from early extubation to the use of a G-suit to improve venous return to the heart. In some centers, a large balloon was placed tightly around the child's lower body and intermittently inflated by a Bird respirator asynchronous with ventilation.

After a couple of years, two innovations changed the outlook. Both were linked to the understanding that a major limitation of the Fontan operation was the need for a normal or near normal PVR to allow survival through the postoperative period when CPB had caused, through release of a variety of inflammatory mediators and cytokines, a marked elevation of PVR in the early postoperative period. When this bypass-related increase in PVR was associated with younger age (<2 years old) at the time a Fontan was attempted, the higher baseline PVR of the infant made the bypass-related PVR worse and resulted in inadequate pulmonary blood flow and (single) ventricular filling in the early postoperative period, leading to a cycle of low cardiac output, pulmonary and systemic edema, further increases in PVR, acidosis, and death.

One solution was to interpose a bidirectional (Glenn) cavopulmonary anastomosis (BDG) 6–12 months before completion of the Fontan operation. This procedure, and the related operation known as a "hemi-Fontan," directed only half of the systemic venous return through the lungs at a time when the infant's PVR had not fallen to normal levels and by preserving an alternative pathway for (single) ventricular filling through systemic venous return not routed through the lungs. This enabled the patients to maintain reasonable cardiac output, although they were a bit "blue" during the early postoperative period, when the PVR had been elevated by CPB. However, this made a third operation, the completion of the Fontan, necessary.

The other innovation was the "fenestrated" Fontan where a small fenestration in the atrial baffle allowed systemic venous return to bypass the lungs as a right-to-left shunt, thereby maintaining ventricular filling and systemic cardiac output during the early postoperative period of high PVR. Over time, the fenestration closed as PVR fell and shunting decreased. Alternatively, a device delivered during an interventional cardiac catheterization could close the fenestrations [52].

This whole process of testing the applicability of the Fontan principle and various modifications of the Fontan operation to a wide variety of types of severe cyanotic CHD involved another set of challenges for the pediatric cardiac anesthesiologist and for collaboration between anesthesiology, cardiology, and surgery. The net result of a great deal of work and collaboration among these groups was that the outlook for the HLHS patients, and indeed for all children with SV defects, improved locally and as these improvements spread and were amplified by work done in other centers, the improvement became national and international. In some institutions, the preferred treatment was and is neonatal transplantation. Its limits are the long waiting time for a transplant, the unavoidable mortality during the waiting period and the ongoing morbidity of neonatal heart transplants, a lifetime of immunosuppression therapy, and the accelerated risk of coronary artery disease seen in heart transplants, even in young children.

The collaboration with pediatric cardiologists around postoperative care of HLHS, Fontan patients, and others spread naturally to the cardiac catheterization laboratory. As pediatric cardiologists began to develop interventional procedures, the need for more control and support of vital functions became apparent. Previously, nurses operating under the supervision of the cardiologist performing the catheterizations had sedated the children for the procedures. In many institutions, this involved high volumes of cases sedated by specially trained nurses, while in others with smaller pediatric caseloads the practice of using general anesthesia for children undergoing cardiac catheterizations had been routine.

The interventional cardiologists turned to pediatric cardiac anesthesiologists for help in managing these patients while the cardiologists themselves were dealing with the complex demands of carrying out interventional procedures in infants and children with CHD. As was the case with newly devised pediatric cardiac surgical procedures, the development of interventional procedures

for CHD in the cardiac catheterization laboratory posed a whole new set of problems and challenges for pediatric cardiac anesthesia. Not the least of these was providing anesthesia and vital function support in the dark and difficult environment of the cardiac catheterization laboratory. The introduction of dilation techniques for pulmonary arteries and veins, and mitral and aortic valves, and, most recently, the dilation of fetal atretic aortic valves *in utero* along with device closure of the PDA, ASD, and VSD all placed progressively greater demands on the anesthesiologists, who became more and more involved in these procedures.

The development of another set of interventional procedures, the use of radiofrequency ablation to deal with arrhythmias in the pediatric patient, illustrates the progressive complexity and difficulty of anesthesia care in these patients. Initially employed only in healthy teenagers with structurally normal hearts but with paroxysmal atrial tachycardia (PAT), anesthesia care was quite straightforward. Now, in contrast, many of these radiofrequency ablation procedures are done in children with complex CHD, repaired or unrepaired, and frequently the children (or adults) may be quite cyanotic or have low cardiac output [49]. At present, in Boston Children's Hospital, the cardiac catheterization laboratory and the cardiac magnetic resonance imaging (MRI) unit perform close to 1,500 anesthesia cases per year.

But despite all those developments, the defects remain the same. If we look at the relative distribution of cases in 1982, 2008, and 2013, we see the same diagnoses and a similar numerical relationship between the major groups. As Helen Taussig remarked in her paper about the global distribution of cardiac diagnoses, only surgical interventions change the numbers [53] (see Table 1.1).

Table 1.1 Cardiovascular surgery at Boston Children's Hospital

	Total cases		
	1982 (*N* = 538)	2008 (*N* = 942)	2013 (*N* = 1,065)
Septal defects	27%	20.1%	23.5%
VSD repair	12%	7.5%	10.4%
ASD repair	9.6%	8.6%	10.1%
CAVC	5.9%	4%	3%
Cavopulmonary connection	3%	8.5%	6.2%
Fontan procedure	3%	5.4%	3%
Bidirectional Glenn		3.1%	3.2%
Systemic outflow obstruction	29%	27.1%	25.8%
Coarctation	7.7%	5.1%	3.4%
Transposition of great arteries		5.6%	3.5%
LVOT repair	11.7%	13.8%	13.4%
Norwood procedure	3%	2.5%	2.3%
Biventricular repair			3.1%
Pulmonary outflow obstruction	13%	18.2%	17.2%
Tetralogy of Fallot repair	7.6%	6.8%	3.9%
Conduit placement/revision	2.8%	2.3%	3.8%
Other RVOT reconstruction	1.6%	9%	9.5%
Pacemaker, AICD placement	5%	3.8%	4.5%
Patent ductus arteriosus	8%	6.2%	7.2%
Miscellaneous	15%	16.1%	15.6%

VSD, ventricular septal defect; ASD, atrial septal defect; CAVC, complete atrioventricular canal; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; AICD, automatic internal cardiac defibrillator.

Emergence of technology, including imaging (TEE, MRI) and ECMO: 2000–2010

The first decade of the 21st century saw many changes driven by the availability of new technology, including transesophageal echocardiography (TEE) and cardiac MRI; these, too, provide new challenges for the pediatric cardiac anesthesiologist.

The utility of TEE in congenital heart surgery was demonstrated in the late 1980s by studies of several groups in Japan and the USA, including Russell and Cahalan at the University of California, San Francisco. The use of two-dimensional echocardiography as well as three-dimensional echocardiography improved diagnosis both within and outside the OR and provided more challenges and opportunities for the pediatric cardiac anesthesiologist.

The TEE interpretation of complex CHD and judgment of the adequacy of intraoperative repairs are considerably more challenging in CHD than in adult acquired heart disease. Many centers have called upon pediatric echocardiographers to make such judgments, rather than the pediatric cardiac anesthesiologist being responsible for that as well as for managing the patient in the post-bypass period. In addition, use of TEE has expanded to the cardiac catheterization laboratory where it is used in parallel with fluoroscopy for device closure of septal defects, allowing confirmation of the placement and location of the device [54]. It has been useful in guiding the mechanical support devices, especially the ventricular assist devices (VAD), confirming cannula placement and the absence of obstruction [55]. The main concerns for the anesthesiologist when using TEE remain airway obstruction, altering left atrial pressure, or even extubating the child in the middle of an operation "under the drapes".

Similarly, the emerging availability of cardiac MRI for diagnosis and follow-up of CHD patients has compounded the difficulties of providing anesthesia and monitoring in an intense magnetic field with limited patient access, but requiring anesthesia to be delivered to patients with severe, complex CHD under difficult conditions. Such technological advances come at a high price and it is hard to see how innovations like the long and expensive search for a method of treatment of HLHS would be justified today.

That decade saw another technical innovation of great importance to pediatric cardiac anesthesia: ECMO (Figure 1.2). Use of rapid-response ECMO for children

Figure 1.2 Infant on extracorporeal membrane oxygenation in the cardiac intensive care unit.

with CHD who suffer cardiopulmonary collapse postoperatively, who cannot be weaned from CPB, or who need to be supported as a bridge to heart transplantation has proved very effective in reducing mortality rates to astonishingly low levels. In the history of the development of pediatric cardiac anesthesia, we have come a long way from the baby in the ice bath being prepared for DHCA to the complex technology necessary for ECMO resuscitation.

This past decade has also seen a pushing of the envelope to devise new surgical and interventional catheterization approaches that cross the boundaries of the traditional care of patients with CHD and these continue to evolve. Two such approaches are transuterine fetal cardiac catheter intervention (see Chapter 15) and hybrid stage I Norwood palliation (see Chapter 25). The hybrid stage I palliation in the catheterization laboratory requires the anesthesiologist to anticipate and treat significant hemodynamic perturbations, blood loss, and arrhythmias during the procedure, while managing neonatal SV physiology without CPB and providing an anesthetic technique that offers the possibility of early tracheal extubation [56,57]. Hybrid procedures are extending in the catheterization laboratory and include VSD closure, HLHS management, and percutaneous valve implantation. They require a multidisciplinary approach and availability of the cardiac interventionists, cardiac surgeon, and anesthesiologist [58].

2011–2015 and the future

With the understanding that certain cardiac lesions are progressive in nature, prenatal intervention is believed to halt the process *in utero* and improve the postnatal outcome of these patients. Since the initiation of fetal cardiac interventions, the number of these procedures has been increasing and includes valvuloplasty of the aortic and pulmonary valve, balloon atrial septostomy for restrictive or intact interatrial septum in cases of HLHS and TGA, and fetal pacing in complete heart block. More than 120 cases have been done at Boston Children's Hospital since 2000 (see Chapter 15). Improving delivery of oxygenated blood to the brain *in utero* may affect neurodevelopmental outcomes of patients with congenital disease – an area of interest and research [59,60]. Pediatric cardiac anesthesiologists have an integral role in designing and carrying out these procedures. Fetal cardiac intervention for aortic valve stenosis or HLHS with intact atrial septum requires the anesthesia team to induce general anesthesia for the pregnant mother, and also analgesia and muscle relaxation for the fetus, with fetal monitoring by ultrasound [61]. The success of the intrauterine procedures allows potential growth of the ventricle with the goal of a biventricular repair during infancy. However, although the reported success of these procedures is promising, the number of cases and series published is small and does not allow us to conclude superiority over neonatal surgeries and discuss long-term outcomes [62,63].

During fetal interventions, anesthesia is most commonly provided to the fetus by intramuscular injection of opioid, muscle relaxant, and atropine. Most studies comparing anesthetics have been done in animal models. Undergoing a prospective clinical trial in a human fetus has multiple limitations, including the limited number and type of procedures, and their associated complications, the maternal condition, and the lack of time to assess the fetal outcomes during the procedure itself [64].

In the past few years, mechanical circulatory support (MCS) has evolved. Although ECMO remains the most widely used MCS among centers, additional ventricular support devices have been used as a bridge to transplant, leading to an increase in the pediatric cardiac transplant waiting lists [65]. The EXCOR® pediatric VAD (Berlin Heart GmbH, The Woodlands, TX, USA) was recently approved by the US Food and Drug Administration (December 2011).

A study database from 2007 to 2011 (the date of approval of the device) compared the 1-year post-transplant survival between patients who underwent heart transplant without VAD support and those who were bridged with EXCOR to transplant. Pediatric patients supported with EXCOR have similar survival rates to Open Procurement and Transplantation Network status 1A patients supported on either inotropes or ventilator [66].

Children with MCS waiting for cardiac transplant may present for multiple surgeries such as line placements, changes of VAD chamber, chest exploration, and laparotomies. Therefore, an understanding of these devices becomes a must and mandates the presence of a pediatric cardiac anesthesiologist in institutions where surgical care is provided to these patients. Challenges include anticoagulation, thromboembolic and cerebrovascular events, and hemodynamic stability [67]. It is important to be familiar with the device and the adjustment of the settings in order to maintain hemodynamic stability. The VAD output is fixed and dependent on volume. Therefore, hypotension is a concern on induction and maintenance of anesthesia, and the most effective therapy is fluid bolus and alpha-receptor agonist. Cave et al.

recommend ketamine as the drug of choice for patients with assist devices [68,69]. A team approach, including surgical, intensivist, anesthesiologist and the mechanical support team, is of the utmost importance for managing these patients and for coordination during the transport to the operating room or the cardiac catheterization laboratory.

As new treatments in CHD are developed by surgeons and cardiologists, and new technology emerges, the pediatric cardiac anesthesiologist faces new challenges. One significant challenge for the current generation of pediatric cardiac anesthesiologists is to help reduce the cost of care. One of the primary ways to reduce perioperative cost is limit ICU and ventilator time. This translates into increased demands and expectations for early extubation, preferably in the OR. Such changes in care have risks associated with them that will require careful assessment considering the advantages achieved with postoperative ventilation and sedation. For example, arrhythmias and cardiac arrest following endotracheal suctioning in the ICU postoperatively almost disappeared when heavy sedation with fentanyl prevented major swings in PA pressure with suctioning [70,71]. Careful selection of patients for early extubation and judicious use of shorter-acting anesthetic agents may allow lengths of stay to be shortened without increasing risks. In some studies, early extubation after relatively simple operations has, in fact, proved to be safe when using new short-acting anesthetic agents such as sevoflurane and remifentanil, particularly when better pain control is also employed. Other advances, such as limiting the total dose of anesthetic agents by developing ways to monitor depth of anesthesia, so as to give sufficient doses to prevent awareness and attenuate stress responses during CPB, are being explored, but remain elusive [72].

In the past, the outcome criterion most emphasized for treatment of CHD was survival. Now that survival rates are very good and getting better for almost all forms of CHD, attention has turned to the quality of that survival. Recent concerns about the effect of anesthetic agents on the developing brain have prompted extensive efforts to study the magnitude of the effect of these agents, the mechanism of the effect, and whether alternative agents or protective strategies are warranted [73]. Neonatal cardiac surgery patients must have surgery at a vulnerable age and also potentially suffer from brain injury from cyanosis, bypass techniques, inflammation, or low cardiac output, and mechanical support devices are a particularly important focus of study. It has been shown that neurodevelopment is impaired in approximately one-third of children who underwent surgery at a neonatal age [74]. As seen on MRI, 23–40% of neonates presenting with a complex cardiac defect show evidence of cerebral injury preoperatively [75–79]. After surgery, 36–73% of patients have evidence of new cerebral lesions on MRI [75–81]. This suggests that much of the injury develops preoperatively. Therefore, cardiac anesthesiologists may play a key role and are involved in research to ameliorate these effects, including brain imaging and long-term neurodevelopmental outcome studies [82–84]. The new American Heart Association/American Academy of Pediatrics guidelines on the evaluation and management of neurodevelopmental outcomes in children with CHD identifies brain biomarkers and EEG measurements that could be useful in managing patients during the perioperative period [85,86].

CHD – a growing specialty from the fetus to the adult patient

Tempora mutantur et nos in illis – "Time changes and we develop with time." It has been 71 years since Robert Gross first ligated a PDA and we have seen amazing developments in the treatment of CHD. Concomitantly, anesthesiology has evolved and slowly defined pediatric anesthesia, and then cardiac anesthesia, and now, in the past two decades, pediatric cardiac anesthesia has developed as a distinct and separate area of subspecialization.

In 2005, the Congenital Cardiac Anesthesia Society (CCAS; www. pedsanesthesia.org/ccas/) in the USA was formed and now has more than 1,100 members. It provides a forum for subspecialized educational meetings, a national database of congenital cardiac anesthesia cases (see Chapter 3), and has initiated an effort to define adequate postgraduate training in pediatric cardiac anesthesia [87] (see Chapter 2). CCAS is a society organized within the larger Society for Pediatric Anesthesia, indicating that this specialty has chosen to align itself more closely with pediatric anesthesiology than with adult cardiac anesthesiology, although there are important common interests and principles in all three of these specialties caring for patients with CHD.

As part of the trend of increasing long-term survival, the patient care group growing most rapidly at most centers is the adult with CHD. The prevalence of adults in the year 2000 was 49% of patients with CHD [88]. This is the somewhat unexpected result as care in childhood improves and more and more of these patients survive to adulthood and even into old age. At many institutions, special programs have been created to treat these patients and the problems they face. These problems include complications, reoperations, and socioeconomic barriers to normal education, employment, and creation of families. The question of pregnancy and anesthetic management of delivery for these patients is also evolving. It is unclear who is most qualified to provide anesthesia for such patients during labor and delivery. But suddenly the pediatric cardiac anesthesiologist may find themselves having to care for adults [89] (see Chapter 16).

Although there has been much progress in pediatric cardiac anesthesia in providing safe anesthetic care and improving the outcome of treatment of CHD in the OR and catheterization laboratory for patients of all ages, much remains to be done. One can say with certainty that the intimate connection between advances in therapy, surgical or medical, and the anesthesia support services

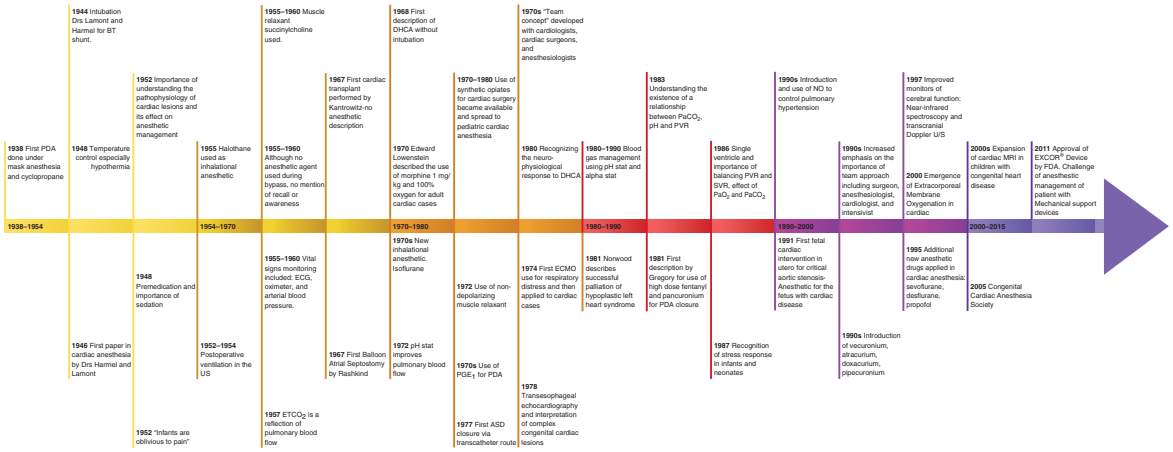

Figure 1.3 Milestones in the anesthetic management of patients with congenital heart disease. BT, Blalock–Taussig; PDA, patent ductus arteriosus; ASD, atrial septal defect US, United States; DHCA, deep hypothermic circulatory arrest; ECG, electrocardiogram; $EtCO_2$, end-tidal carbon dioxide; ECMO, extracorporeal membrane oxygenation; PCO_2, partial pressure of carbon dioxide; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; NO, inhaled nitric oxide; U/S, ultrasound; MRI, magnetic resonance imaging; EXCOR, extracorporeal ventricular assist device; FDA, Food and Drug Administration.

required to make those therapeutic advances possible will continue to present new challenges to the pediatric cardiac anesthesiologist. (Figure 1.3) The pediatric cardiac anesthesiologists will, in turn, meet those challenges and in the process find ways to make yet more improvements. Thus we progress in our art and science.

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A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 2

Education for Anesthesia in Patients with Congenital Cardiac Disease

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Introduction

Advances in diagnosis in pediatric cardiology, medical management, cardiac surgery, and cardiac anesthesia throughout the world have drastically increased the survival rate of children with congenital heart disease (CHD) to over 90% and, as a result, there are more adults than children living with CHD today. However, although the heart condition is treated at a young age, the defect is usually considered chronic due to the possibility of increased health issues as a result of experiences or restrictions related to the heart disease itself. The need for greater coordination and integration between pediatric and adult services and a long-term healthcare delivery system is obvious for this patient population. Unfortunately, after leaving pediatric cardiology, many patients are lost to follow-up errors. The specific type of program needed to better ensure all of these patients are "found" and better treated is yet to be discovered, but structured education for adolescents (and their parents), explaining the importance of follow-up, is a vital component.

Anesthesiologists, as an integral part of any system caring for patients with CHD, are often called upon to care for patients ranging in age from neonates to adults. Before the advent of the Congenital Cardiac Anesthesia Society (CCAS) in 2005, there were very few resources in terms of providing training and experience in the specific field of pediatric cardiac anesthesia. The board of directors along with other pediatric anesthesiologists addressed the lack of training criteria in congenital cardiac anesthesia both in the United States and internationally and have developed the resources that we have today.

Why teach and learn congenital cardiac anesthesia?

Only very recently has a curriculum for education in the care of patients with CHD been suggested [1]. Establishment of a curriculum had been complicated by the fact that very few anesthesiologists engage in a practice limited solely to the care of pediatric patients undergoing cardiac surgery. By necessity, most pediatric cardiothoracic anesthesiologists devote some portion of their time to the care of general pediatric patients or to the care of adult cardiothoracic surgical patients. Furthermore, while it has been widely regarded since the 1990s that intraoperative transesophageal echocardiography (TEE) is an accepted standard for the adult cardiac anesthetist, at present there is no formal examination or certification process for pediatric TEE and there is a debate about who (cardiologist or anesthesiologist) is best qualified to perform perioperative pediatric TEE.

The current model

Currently, teaching and learning in congenital cardiothoracic anesthesia more closely resemble an apprenticeship

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model than an established training program. This model has not changed over recent years. Most of this training occurs in a few centers across the US. The type of training received and quality of education are not yet standardized in spite of the efforts taken by these centers of excellence. The "apprenticeship model" as currently practiced does not utilize a structured approach that involves advocating teaching behaviors such as modeling, creating a safe learning environment, coaching, knowledge articulation, and exploration.

A recent publication by the Johns Hopkins group looked at pediatric urology training across the US. This specialty has traditionally used the apprenticeship model. They surveyed 44 pediatric urologists who had completed the 2-year Accreditation Council for Graduate Medical Education (ACGME) approved fellowships and concluded that pediatric urologists feel prepared in commonly performed procedures and perioperative care. The surgeons surveyed reported that faculty feedback/supervision, independent reading, and conferences were rated as a very effective method of teaching.

Saperson discusses the value of changing an apprenticeship model of teaching and educating in psychiatry in Canada to a more competency-based education with explicit expectations. Magen et al. discuss the importance of restructuring training in psychiatry in the US in relation to the healthcare environment. They speculate that funding for graduate medical education programs may be determined by quality measures.

Leong et al. recently completed a survey of pediatric pulmonologists to determine how flexible bronchoscopy is taught to trainees. Based on their survey results, they plan to build a formal competency-based curriculum. Pediatric cardiac surgeons have also recognized that the model to teach trainees to successfully cannulate a pediatric patient for extracorporeal membrane oxygenation (ECMO) based on the apprenticeship model is inadequate. Allan et al. have developed a simulation-based curriculum where they used time to cannulation as a primary endpoint to measure competency [7].

Most trainees also learn from their "role models" in the operating room (OR). In role modeling, faculty members demonstrate clinical skills, and model and articulate expert thought processes. Passi et al. question the value of role modeling in medical education and have conducted an extensive review of the literature to assess the effectiveness of this technique.

Curriculum for learning and teaching congenital cardiac anesthesia

Curriculum development should employ a logical, systematic approach linked to specific healthcare needs. The Kern model of curriculum development for medical education could be used to develop a curriculum to teach and learn congenital cardiothoracic anesthesia [9]. This is a six-step approach and consists of the following:

1. Problem identification and general needs assessment
2. Targeted needs assessment
3. Goals and objectives
4. Educational strategies
5. Implementation
6. Evaluation and feedback.

Problem identification and general needs assessment

This comprises identification and characterization of the healthcare problem:

- Whom does it affect?
- What does it affect?
- What is the qualitative and quantitative importance of the effects?

Education in anesthesia for CHD covers a wide range of lesions – uncorrected, corrected, and palliative therapies. The trainee needs to be educated in all aspects of the six core competencies related to these topics. This is often a daunting task for the educator as well as the trainee. Most traditionally trained pediatric anesthesiologists and adult cardiothoracic anesthesiologists do not have the expertise to manage the unique set of problems presented by this diverse patient population. Although a relationship of clinical outcomes to the training and education level of the healthcare provider has yet to be demonstrated, there is still the potential for a structured curriculum to positively impact quality of care and allocation of healthcare resources. van der Leeuw et al. completed a systematic review of the effect of resident training on patient outcome. They concluded that with adequate supervision, contingencies for additional OR time, and evaluation of and attention to the individual competence of residents throughout residency training could positively serve patient outcomes. There is limited evidence available on the effect of residency training on later practice.

The following points should be addressed to obtain adequate needs assessment:

- What proficiencies (cognitive, affective, and psychomotor skills) currently exist among learners?
- Previous training and experiences of fellows and residents in congenital cardiac anesthesia
- Current training and experiences already planned for trainees
- Resources available to learners (patients and clinical experiences, information resources, computers, audiovisual equipment, role models, teachers, mentors)
- Perceived deficiencies and learning needs
- Characteristics of the learners and barriers to learn and teach.

The current state of anesthesiology training in CHD has recently been characterized in a telephone and email survey performed in 2008 of anesthesia residency program directors (n = 131), ACGME-accredited pediatric anesthesia fellowship directors (n = 45), adult cardiothoracic anesthesia fellowship directors (n = 71; 44 ACGME-accredited, 27 non-ACGME-accredited), and

12-month pediatric cardiac anesthesia fellowship training program directors (n = 3). The following responses summarize training in the USA [1]. Hands-on experience with pediatric cardiac anesthesia during basic anesthesia training is described as "nonexistent" or "rare" in 50% of ACGME-accredited residency programs. In the remaining programs, typical exposure is during the CA-2 and CA-3 years, with residents caring for five to 10 patients requiring procedures with cardiopulmonary bypass (CPB). In a few programs, residents care for as many as 20–30 such patients. Pediatric anesthesia fellows in all 45 ACGME-accredited programs have at least a 2-month cardiac experience during the 12-month fellowship. The typical fellowship experience involves 30–50 CPB cases. In two-thirds of the programs this exposure occurs in 1-month blocks, and in the remainder the experience is distributed throughout the year. Approximately one-quarter of the pediatric fellows use elective time to obtain an additional month or two of experience. Presently, only 13 of the 44 ACGME-accredited and one of the 27 non-accredited fellowships in adult cardiothoracic anesthesia have a mandatory exposure to pediatric cardiac anesthesia, with the remaining programs offering an elective experience of varying duration. Typical mandatory exposure is 1–2 months with 20–30 CPB cases. The words "rarely" or "occasionally" were most commonly used by the individuals surveyed to describe the frequency with which adult cardiothoracic anesthesia fellows use available elective time to pursue training in pediatric cardiac anesthesia. Besides the three known 12-month pediatric cardiac anesthesia fellowships (two in the USA, one in the UK), there were several programs in the USA that offer additional training in pediatric cardiac anesthesia for intervals of 3–12 months on an ad hoc basis.

By 2012, a Second Year Advanced Pediatric Anesthesiology Fellowship Network had been formed in the US, through the efforts of the Pediatric Anesthesia Leadership Council and the Pediatric Anesthesia Fellowship Program Directors' Association. Pediatric cardiac anesthesia advanced fellowships were included, and a 12-month training period was specified. As of that time, 18 programs were offering these fellowships with a total of 22 available positions.

There is no formal education in TEE at this time for a fellow training in pediatric cardiac anesthesia. This is a skill that is mandated of an adult cardiac anesthesiologist. The model as it stands today in most centers in the US calls for the cardiologist to be in the OR providing the expertise necessary to make intraoperative decisions. It is not currently an expectation that the pediatric cardiac anesthesiologist will have this skill. The question arises as to who is best suited to perform the TEE in the OR. The other question that needs to be answered is how perioperative TEE education will be incorporated into the training model. Will the National Board of Echocardiography devise goals and objectives and a formal assessment of competency?

Targeted needs assessment

For the needs assessment to be an accurate reflection of what is required, it must involve the current trainees (learners) in pediatric cardiac anesthesia. Attempts should be made to assess the current strengths and weaknesses in knowledge, skills, and performance [13]. The environment in which the education is currently happening needs to be evaluated as well. Is the OR conducive to education of some of the complex physiology or should the initial education happen in a simulated environment where the stress level of all concerned is much lower? It is vital that all the stakeholders (trainees, program directors, cardiologists, intensivists and pediatric cardiac surgeons) are involved in the development at an early stage. Barriers and reinforcing factors that affect learning should be identified early on. Faculty development programs may be necessary to improve the quality of teaching and education in congenital cardiac anesthesia. Needs assessment should also include what resources are currently available to the trainees to facilitate learning in congenital cardiac anesthesia. The case mix in the training programs, multidisciplinary faculty educators, and access to online journals and educational materials, including the availability of audiovisual equipment, are vital to the success of curricular delivery. The value of the hidden and informal curriculum that is currently in place should not be underestimated.

To date, there have been no reports of needs assessment for curriculum development in congenital cardiac anesthesia in the medical literature. Such an initial needs assessment could be accomplished in the form of a Delphi system, in which global expert opinion as to curriculum needs is sought. This would be an economical method of accessing experts in the field and imposes few geographical limitations. Schinasi et al. used a simulation-based model to perform a needs assessment in procedural sedation among pediatric residents. A study by Haji et al. reported needs assessment for simulation training in neuroendoscopy. The nominal group technique (also known as the expert panel) and the consensus development conference could also be utilized; however, these methodologies are more difficult to organize and are time consuming. Focused group discussions at the annual meeting of the Society for Cardiovascular Anesthesiologists or Society for Pediatric Anesthesia will help deepen information obtained. However a skilled facilitator and note taker are essential so everyone is allowed to voice their opinion and accurate information is recorded. Consideration should be given to the use of the Curriculum Management and Information Tool that is made available by the American Association of Medical Colleges to all medical school faculty. The ultimate goal of the developed curriculum would be to reference objectives, competencies and/or learning outcomes in congenital cardiac anesthesia.

Goals and objectives

Goals and objectives must, by necessity, be specific and measurable. They should measure the knowledge (cognitive), attitude (affective), and competence (psychomotor) of the learners. The goals and objectives can be developed on the basis of the ACGME core competencies suggested for residency programs. The goals and objectives should reflect the relationship of the educational process to the degree of participation of the learners, as well as the faculty response to the developed curriculum. To achieve goals, the program must be structured to ensure optimal patient care while providing trainees with the opportunity to develop skills in clinical care, judgment, teaching, and research. Consideration should be given to the use of learning goal-scoring rubrics. Meyerson et al. performed a needs assessment for an errors-based curriculum on thoracoscopic lobectomy and structured the curriculum based on their observations using a standardized checklist.

The following goals and objectives are valuable in the OR to achieve competency in congenital cardiac anesthesia:

- The subspecialist in congenital cardiac anesthesiology should be proficient in providing anesthesia care for both pediatric and adult patients undergoing congenital cardiac and vascular surgery as well as anesthesia for non-cardiac surgery.
- The subspecialist should demonstrate and conduct a preoperative patient evaluation; and demonstrate the ability to interpret imaging, cardiovascular, and pulmonary diagnostic test data.
- The subspecialist should be able to evaluate and understand the anesthetic management of patients undergoing non-operative diagnostic and interventional cardiac, thoracic, and electrophysiological procedures. Examples include angiography, arrhythmia mapping and ablation, stent placements, and device closures.
- The clinical curriculum should include competency and demonstrate cognitive proficiency in the management of CPB, pharmacological and mechanical hemodynamic support as well as extracorporeal circulation.
- An advanced skill level in perioperative TEE should be developed and demonstrated as measured by acceptable scores on standardized testing. This skill should be applied on a regular basis in clinical situations and there should be a plan to demonstrate ongoing continuing education in advanced TEE.
- The subspecialist should be able to create a plan for postoperative critical care, including ventilatory support, extracorporeal circulatory support, and pharmacologic hemodynamic support, as well as understand the implications of pain management.
- The subspecialist should demonstrate effective communication skills in obtaining informed consent from families, discussing any complications that may have occurred as well as providing consultations as and when necessary.
- The subspecialist should demonstrate skills in preparing materials and presenting at multidisciplinary conferences to allied health professionals.
- The subspecialist must demonstrate professionalism in the work environment as evidenced by the ability to show compassionate care to the patient and their diverse needs, respecting other providers, as well as complying with program, department, and institutional policies and procedures.
- The subspecialist should understand the value of multidisciplinary teams, be able to evaluate errors, and find solutions, thereby enhancing patient safety and improving outcomes for their patients.

The didactic curriculum provided through lectures, conferences, and workshops should supplement clinical experience as necessary for the fellow to acquire the knowledge to care for cardiothoracic patients with CHD and conditions outlined in the guidelines for the minimum clinical experience for each fellow. The didactic components should include the areas in the following list, with an emphasis on how cardiothoracic diseases affect the administration of anesthesia and life support to cardiothoracic patients with CHD.

These represent guidelines for the minimum didactic experience for each fellow:

- Embryological and morphological development of the cardiothoracic structures; nomenclature of CHD
- Pathophysiology, pharmacology, and clinical management of patients with all adult and pediatric CHD, including single ventricle lesions, septal defects, defects of semilunar and atrioventricular valves, left- and right-sided obstructive lesions, transposition of the great vessels, defects of systemic and pulmonary venous return, cardiomyopathies, vascular rings and tracheal lesions
- Pathophysiology, pharmacology, and clinical management of patients requiring heart, lung, and heart–lung transplantation, including immunosuppressant regimes and selection criteria
- Non-invasive cardiovascular evaluation: electrocardiography, echocardiography, cardiovascular computed tomography (CT), and magnetic resonance imaging (MRI)
- Cardiac catheterization procedures and diagnostic interpretation; invasive cardiac catheterization procedures, including balloon dilatations and stent placement; device closure of septal defects, patent ductus arteriosus and baffle leaks, and arrhythmia ablation
- Pre-anesthetic evaluation and preparation of pediatric and adult cardiothoracic patients
- Pharmacokinetics and pharmacodynamics of medications prescribed for medical management of pediatric and adult cardiothoracic patients
- Peri-anesthetic monitoring methods, both non-invasive and invasive, including use of ultrasound guidance: intra-arterial, central venous, mixed venous saturation, cardiac output determination, transesophageal and epicardial echocardiography, neurological monitoring,

including near-infrared cerebral oximetry, transcranial Doppler, and processed electroencephalograms
- Pharmacokinetics and pharmacodynamics of anesthetic medications prescribed for cardiothoracic patients. Pharmacokinetics and pharmacodynamics of medications prescribed for management of hemodynamic instability: inotropes, chronotropes, vasoconstrictors, vasodilators
- Extracorporeal circulation (including CPB, low-flow CPB, deep hypothermic circulatory arrest, antegrade cerebral perfusion, ECMO), myocardial preservation, effects of extracorporeal circulation on pharmacokinetics and pharmacodynamics, cardiothoracic, respiratory, neurological, metabolic, endocrine, hematological, renal, and thermoregulatory effects of extracorporeal circulation and coagulation/anticoagulation before, during, and after extracorporeal circulation
- Circulatory assist devices: left and right ventricular assist devices and biventricular assist devices
- Pacemaker and automated internal cardiac defibrillator (AICD) insertion and modes of action
- Perioperative ventilator management: intraoperative anesthetic and critical care unit ventilators and techniques
- Pain management of pediatric and adult cardiothoracic surgical patients. Post-anesthetic critical care of pediatric and adult cardiothoracic surgical patients
- Research methodology and statistical analysis
- Quality assurance and improvement
- Ethical and legal issues
- Practice management.

What is the minimum level of anesthesia training required?

- Subspecialty training in congenital cardiac anesthesiology should begin after satisfactory completion of a residency program in anesthesiology accredited by the ACGME or other training judged suitable by the program director. This track would be consistent with other subspecialty training areas in anesthesiology.
- Trainees could enter the training following completion of an ACGME-accredited adult cardiothoracic anesthesia fellowship of 12 months' duration after anesthesia residency.
- Trainees could enter the training following completion of an ACGME-accredited pediatric anesthesia fellowship of 12 months' duration after anesthesia residency.
- Subspecialty training in congenital cardiac anesthesiology could be part of an 18-month continuum in conjunction with an ACGME-accredited pediatric anesthesia fellowship or adult cardiothoracic anesthesiology fellowship after successful completion of an anesthesia residency.
- Recent recommendations as part of the Second Year Advanced Pediatric Anesthesiology Fellowship Network specify a minimum of 12 months of congenital cardiac anesthesiology fellowship training following the 12-month ACGME first-year pediatric anesthesiology fellowship.

What are the ideal duration, case quantity, and scope of training?

The following represent suggested guidelines for the minimum clinical scope and duration of training:
- Nine months of clinical anesthesia activity caring for patients with congenital cardiac problems in the OR, the cardiac catheterization laboratory, and other locations.
- This experience should include a minimum of 100 anesthetic procedures, the majority of which must require CPB. At least 50 of these patients should be infants from birth to 1 year of age, and should include at least 25 neonates (≤1 month of age). The trainee should also care for at least 25 adults (≥18 years of age).
- This experience should also include a minimum of 50 patients undergoing diagnostic procedures (cardiac catheterization, echocardiography, MRI, etc.), as well as therapeutic procedures in the catheterization laboratory (arrhythmia ablation, pacemaker insertion, septal defect closure and valve dilatation, etc.).
- This experience should include a structured intraoperative TEE experience consistent with the practice of intraoperative TEE in the participating program.
- Fellows entering the congenital cardiac anesthesia fellowship following completion of an adult cardiothoracic anesthesia fellowship must complete a 3-month rotation caring for children in the general, non-cardiac ORs to enhance their pediatric anesthesia skills.
- Fellows entering the congenital cardiac anesthesia fellowship following completion of a pediatric anesthesia fellowship or as part of the 18-month congenital cardiothoracic anesthesiology program will complete:
  - A 2-month experience managing pediatric cardiothoracic surgical patients in a critical care (ICU) setting. This experience may include the management of non-surgical cardiothoracic patients. The fellow should actively participate in the management of patients on ECMO.
  - One month of elective rotations (none less than 2 weeks in duration) from the following categories:
    - Echocardiography (TEE and/or transthoracic echocardiography)
    - Extracorporeal perfusion technology
    - Research.
- Experience should be obtained in the preoperative evaluation of pediatric and adult cardiothoracic patients.
- The fellow should understand how to use information from diagnostic studies and how to recognize when additional studies and/or consultations are indicated.

Relationship to other anesthesiology programs

The congenital cardiac anesthesiology program should function in direct association with an ACGME- accredited core anesthesiology program, adult cardiothoracic

anesthesiology, or a pediatric anesthesiology program. A congenital cardiac anesthesiology program may be conducted in either a general hospital or a children's hospital. There must be within the same institution as a fully accredited core anesthesiology program or an adult cardiothoracic anesthesiology program or pediatric anesthesiology program with which the congenital cardiac anesthesiology program is associated. The division of responsibilities between trainees in the core anesthesiology program and an associated fellowship program(s) in adult cardiothoracic anesthesiology and/or pediatric anesthesiology must be clearly delineated. The presence of congenital cardiac anesthesiology fellows must not compromise the clinical experience and number of cases available to pediatric anesthesiology fellows and/or core anesthesiology residents. There must be close cooperation between the core anesthesiology program, the adult cardiothoracic anesthesiology program and/or the pediatric anesthesiology program, and the congenital cardiac anesthesiology program.

Educational strategies

Educational strategies involve the content of materials to be delivered in setting of the curriculum as well as the instructional methodology to be used to deliver the content. It will be beneficial to have the fellows involved in the planning of the educational activity. Consideration should be given to forming a committee of responsible faculty members to ensure that the best possible content is delivered.

Content of the curriculum

The driving force here is the learning objectives that have been created in the goals and objectives section. The program director should consider development of a syllabus that includes learning objectives for the lectures, locations of the lectures, any readings that may have to be completed prior to arrival at the educational activity as well as additional resources for the educational activity. All of this information could be made available on a departmental intranet so the fellows have access to it at all times of the day.

Educational methodology

To thrive in today's technologically complex and information-laden clinical environment, pediatric cardiac anesthesiology trainees must become self-directed learners who are able to engage in self-reflection and assessment of their learning needs. To facilitate self-directed learning, program directors and trainees should work together to develop individualized educational plans, learning contracts, and milestone timelines. Here is a list of suggested educational strategies that may be used to address the cognitive, affective, and psychomotor objectives of the curriculum:

- Strategies for achieving cognitive objectives
  - Readings
  - Lectures or large group interactive discussions
  - Audiovisual materials
  - Small group discussions
  - Self-study modules or web-based learning materials
  - Online discussion forums
  - Podcasts or streaming video
  - Fellow-led didactic sessions
  - Systematic reading of stored TEE clips, if included in the curriculum
- Strategies for achieving affective objectives
  - Exposure to, and discussion of, challenging clinical and ethical situations
  - Simulated-learning and cross-training experiences with facilitated debriefing to gain experience in leadership, communication, task delegation, and team development skills
  - Facilitation and modeling of openness, introspection, and reflection through establishment of a safe learning environment
  - Observation of role models, and serving as a role model for anesthesiology residents
  - Standardized patients and role plays
- Strategies for achieving psychomotor objectives
  - Regular supervised clinical experiences with feedback
  - Simulations: partial task trainers, full-body manikins, virtual reality simulators
  - Audiovisual reviews of skills
  - Expert-derived checklists of procedural competence.

In the digital age, there are several tools available to deliver content to the learners. However, all the different methods available may not be suitable for the various objectives to be achieved. Use of self-directed readings, lectures, programmed learning, small group discussions, problem-based discussions, and learning projects is helpful to advance cognitive knowledge. Team-based training, problem-based learning and participation in learning projects all help to cultivate problem-solving skills. However, to teach some of the affective objectives, reflective exercises, discussions and observing role models in the OR may be helpful. To teach skills or competency objectives, the trainee may be taught using simulations, using standardized patients, supervised clinical experiences, artificial models and role playing. All these methods of teaching have pros and cons. They have to be adapted for each individual program and only serve as a guide for program directors. The ideal methodology will encourage active learning, provide immediate feedback to the trainee, promote learning from experience, provide a safe learning environment, facilitate learning of higher cognitive objectives, and promote trainee motivation and responsibility. Utilization of low-cost and less resource-heavy methodologies is also more likely to succeed. Consideration should be given to faculty development if new instructional methodologies are to be utilized.

Conferences should be regularly attended by the trainee, including lectures, interactive conferences, hands-on workshops, morbidity and mortality conferences, cardiac catheterization conferences, echocardiography conferences, cardiothoracic surgery case review conferences, journal reviews, and research seminars. While the faculty

members should be the leaders of the majority of the sessions, active participation by the fellow in the planning and production of these conferences is essential. Attendance at multidisciplinary conferences, especially in cardiovascular medicine, pulmonary medicine, cardiothoracic surgery, vascular surgery, and pediatrics relevant to cardiothoracic anesthesiology, should be encouraged. Provision of an opportunity for fellows to participate in research or other scholarly activities is vital to the success of the educational strategies employed. The fellows must be encouraged to complete a minimum of one academic assignment. Projects may include grand rounds presentations, preparation and publication of review articles, book chapters, and manuals for teaching or clinical practice, clinical research investigation, or similar scholarly activities. A faculty supervisor must be in charge of each project.

In the context of practice-based learning and improvement, trainees should be encouraged to participate in audits of their own patient care and be involved in critical appraisal of clinical practices and the literature. Trainees should be encouraged to develop learning portfolios as well as to create a learning plan for themselves. Learner-driven teaching methodologies are likely to be more successful.

Congenital cardiac anesthesia lends itself nicely to education in the various aspects of systems-based practice and teamwork. Trainees should be involved with quality improvement and attend case conferences focused on cost-effectiveness, patient saftey and quality of care as part of a multidisciplinary team. In situ team training has been associated with improved patient outcomes in the setting of pediatric emergencies.

Explicit education in professionalism in the cardiothoracic OR should be promoted by educating the trainees using faculty role models, trainee participation in writing professionalism goals and objectives, and trainee participation in ethics rounds in the intensive care unit (ICU) as part of a mutlidisciplinary team.

Advances in the Internet have created a number of opportunities for educational material to be easily shared. Most of the content material developed could be posted on the Internet with password-protected access. As the number of physicians training to be providers of anesthesia for CHD is small, this option is attractive. Interesting case discussions, sharing of echocardiographic images, and recent articles pertaining to this area could be posted on the Internet as well. The MedEdPORTAL, Health Education Assets Library (HEAL), CCAS website, and Multimedia Educational Resource for Learning and Online Teaching are some currently available resources that could house the curricular material related to congenital cardiac anesthesia. However, given this wealth of potential educational resources, it is important to keep in mind that the learner should be physically and mentally involved in the learning process. Despite this wealth of potential educational resources, however, it is unclear to what degree anesthesia teachers use these resources as part of their teaching or curricula.

The use of simulation in medical education is also gaining popularity. Simulation allows complex clinical tasks to be broken down into their component parts. Simulation-based medical education can contribute considerably to improving medical care by boosting medical professionals' performance and enhancing patient safety. Many surgical specialties are looking to simulation as a method for teaching and learning as well as evaluation. There is a role for simulation in learning procedural skills, especially in the climate of decreasing clinical exposure. Recent meta-analysis of the use of simulation in anesthesia training showed inconsistency in measurement of non-technical skills and consistency in the (ineffective) design of debriefing [23]. There is also evidence in the surgical literature that virtual reality training can improve OR performance. In a recent meta-analysis, a simulation-based airway management curriculum appeared superior to no intervention and non-simulation intervention for important education outcomes. Consideration should be given to the use of a clinical skills laboratory to pre-teach some of the skills necessary in the management of a complex patient population [25].

Anesthesia for CHD is a high-risk, low-error tolerance field. The fundamental knowledge and skills that congenital cardiac anesthesiologists will need to master if they are to increase their capacity to attain higher levels of performance are considerable. A clinical microsystems model may prove useful to facilitate the development of this fundamental knowledge and skills using the action-learning theory and sound education principles to provide the opportunity to learn, test, and gain some degree of mastery.

Implementation

Once a curriculum has been developed, it is the role of the program director to oversee its successful implementation. Success is achieved through insightful leadership, transparency and constant communication, forethought and general administration of the program, continuous quality improvement efforts, and establishment and maintenance of a stable educational environment. The program director must possess the requisite specialty expertise and have training and/or clinical experience in providing anesthesia care for congenital cardiac surgical patients that meets or exceeds that associated with completion of a 1-year congenital cardiac anesthesiology fellowship program. To implement a new curriculum, the program director must possess the necessary administrative and educational knowledge and skills to:

- identify necessary materials and resources
- obtain administrative and, if necessary, financial support
- identify and recruit qualified faculty members
- provide faculty development and teacher training
- develop administrative mechanisms to support the curriculum
- identify appropriate teaching space (e.g. in the OR, simulation center, or other appropriate clinical venues)
- anticipate and address barriers.

Above all else, the program director is responsible for keeping faculty, learners, and staff informed about plans for implementing a new curriculum. Individuals who are expected to support, teach, or participate in program must be made aware of the program's design, educational strategies, and assessment methods in order to ensure its smooth execution. The program director should also present curricular updates, especially any successes or milestones achieved, to identified stakeholders. Stakeholders are people with an interest in the program and its evaluation and may include the pediatric anesthesia department chair, cardiothoracic anesthesia division chief, anesthesia residency program director, other anesthesia subspecialty fellowship directors, funding agencies, and/or hospital administrators (e.g. the Vice President for Quality and Safety).

While the program director is responsible for overseeing the curriculum, this does not have to be done in isolation. There are a number of faculty and staff members who can provide support and advice regarding the design and teaching of a curriculum. As an added benefit, those involved at the front end of a program's design and implementation are more likely to want to participate in teaching and assessing the curriculum. A junior faculty member with expertise in congenital cardiac anesthesiology and interest in medical education may be eager to help develop and present a curriculum. Pediatric anesthesia faculty members with previous curriculum development experience as well as clinician educators committed to anesthesiology training in CHD may be recruited as educational consultants and then later asked to teach in the program. Involving other faculty members in the development and implementation of a curriculum also ensures a program's continuity, stability, and sustainability.

There are several key decisions that must be made, and steps that must be taken, before implementing a congenital cardiac anesthesia curriculum. First the program director needs to decide whether to introduce the curriculum as a pilot program, in stages, or to present it in its entirety. There are arguments for and against each approach; however, if stakeholders are wary of a new curriculum's educational benefit, it is best to introduce a pilot program in order to collect evidence of its value and then gain support for its full implementation. Recruiting faculty members and then developing them to teach in the program are further essential steps. To present a successful and sustainable curriculum, there must be a sufficient number of faculty members with documented qualifications to instruct and adequately supervise all anesthesia fellows in the program. Although the number of faculty members involved in teaching will vary, there should be at least three and these should be equal to or greater than two full-time equivalents, including the program director. A ratio of no less than one full-time equivalent faculty member to one subspecialty fellow must be maintained. The anesthesia faculty must possess the requisite congenital cardiac anesthesia specialty expertise, competence in clinical care, and teaching abilities, as well as documented educational and administrative abilities and experience in their field. There must be evidence of active participation by qualified physicians with training and/or expertise in congenital cardiac anesthesiology beyond the requirement for completion of a core anesthesiology residency. The faculty members should have training and experience that would generally meet or exceed that associated with the completion of a 1-year congenital cardiac anesthesiology program. Faculty members in cardiology, cardiothoracic surgery, pediatrics, intensive care, and pulmonary medicine can provide teaching in multidisciplinary conferences. The responsibility for establishing and maintaining an environment of inquiry and scholarship of discovery, dissemination, and application rests with the program director and the faculty, and an active research component must be included in each program.

Equally important to recruiting qualified faculty members with the appropriate expertise and training in congenital cardiac anesthesiology is developing their ability to teach the curriculum. It is a common error to assume that faculty members with the necessary clinical skills, knowledge, and specialty expertise are also qualified to teach. Rarely are they required to provide documentation of their teaching experience or evidence of teacher training, even for the most basic skills such as assessing and providing feedback to learners, leaving many ill-prepared for their teaching responsibilities. The core components of a faculty development program in training congenital cardiac anesthesiology fellows should include:

- Communication of curricular goals and objectives
- Discussion of qualities that characterize effective and respected clinical educators
- Suggestions of how to apply adult learning principles to congenital cardiac anesthesia clinical venues
- Assurance that faculty members can effectively assess trainees and provide useful feedback on their performance
- Review of best teaching practices for common educational strategies such as procedural teaching as well as large and small group facilitation skills
- Specialized training sessions to teach faculty members how to communicate and explain clinical decision-making; make teaching in the OR a priority; maintain a balance between supervision and autonomy; promote critical thinking skills; and provide clear, constructive, and developmental feedback.

Evaluation and feedback

Evaluation and feedback are essential for the continuous improvement and development of a curriculum. The purpose of evaluation in medical education is to determine if the curricular goals and objectives were met. In addition, an evaluation can determine if the time, resources, and effort spent producing the curriculum are merited. Evaluation results can be used to identify educational outcomes, assess teaching effectiveness, determine areas of strength and needed improvement, and make decisions about the

level of support necessary to sustain or further develop a curriculum. "Feedback" is defined as the provision of information regarding an individual's or program's performance to trainees, faculty, stakeholders, and accrediting agencies. While the terms "evaluation" and "assessment" are often used interchangeably when measuring both individual learner and program outcomes, it is best to distinguish between them, adopting the term "evaluation" in relation to measurement of the curriculum, and "assessment" in relation to the measurement of learners. As learner assessment often comprises a significant portion of a program's evaluation, making this distinction will help to avoid confusion when planning and presenting results [28].

The process of curriculum evaluation and feedback

To conduct a comprehensive evaluation of a congenital cardiac anesthesiology program, multiple sources of data must be sought, which requires a systematic information collection process involving learners, faculty, other healthcare providers, and, in some cases, external evaluators. Data and information should be collected at the start of a curriculum, and also at its midpoint, conclusion, and subsequent to completion (e.g. 6–12 months post-fellowship). A program director's effort in collecting evaluation data at the program's mid- and endpoints will be less challenging if the requisite time and effort are put into creating specific and measurable learning objectives at the start of a curriculum, and into assessing the fellows' knowledge, skills, and performance levels in congenital cardiac anesthesiology up-front. With the appropriate administrative support, a program director can institute an iterative "plan–do–check–act" methodological approach to continuous curriculum improvement. This method involves *planning* (the curriculum development steps 1 through 4 – problem identification through educational strategies); *doing* (the implementation step); *checking*, in which data are collected to determine what is going well and what needs to be improved moving forward; and *acting*, in which the program director addresses identified curricular problems by determining their causes and applying countermeasures, standardizes what is working well, and communicates decisions, new standards and improvements to be made.

Kirkpatrick described four levels to focus program evaluation, which Curran and Fleet later adapted for use in medical education evaluation:

- Reaction – this level of evaluation is intended to evaluate how well participants liked a program. It generally provides data concerning participants' perceptions, and satisfaction with objectives, content, instruction, delivery, and/or instructors.
- Learning outcomes – this level of evaluation involves some form of assessment of changes in skills, knowledge, or attitudes among learners; it is most commonly conducted through pre- and post-test study designs.
- Performance improvement – this level of evaluation provides information on the extent to which learning has influenced the post-learning behavior or performance of learners in their practice setting. Evaluating at this level attempts to answer the question: Are the newly acquired skills, knowledge, or attitudes being used in the everyday environment of the learner?
- Patient/health outcomes – this level of evaluation is concerned with measuring tangible results which are influenced by the performance of the learner as a result of participation in the education activity. These tangible results can be transferred to a health perspective (e.g. improving patient health or improving efficiencies). Evaluation at this level is challenging given the variety of uncontrollable variables a learner encounters when he or she leaves an educational program.

A program director needs first to determine the intention of the curriculum evaluation as well as the audience reviewing the results in order to choose which level(s) to focus his or her time and effort on. For example, if a department chair is mostly interested in whether the fellows are better able to perform advanced TEE in the OR, then evaluation results should report on learning outcomes. If, however, the Vice President of Healthcare Quality is interested to report to the board on the reduction of anesthesia-related complications post-CHD surgery, then the focus should be on patient/health outcomes.

Learner assessment methods

With the adoption of outcomes-based training requirements in 2002, the focus of learner assessment for all residency programs has been on the ACGME's six core competencies. The goal of competency-based assessment is for trainees to meet discreet, transparent, achievable objectives at developmentally appropriate stages in training. The challenge for program directors of congenital cardiac anesthesia training programs is to ensure that the curriculum's goals and objectives match the intended competencies. As Ebert and Fox [33] note:

> "To establish competence in congenital cardiac anesthesia could mean standardized classroom teaching, followed by defined experiences in the clinical setting. For example: The fellow's progression of skills and knowledge of TEE, aortic balloon pumps, left ventricular assist devices, on-and-off pump procedures, management of hemodynamics in patients with complex valve abnormalities, right heart failure, pulmonary hypertension, and significant arrhythmias would be carefully structured. If the opportunity did not present itself in the clinical setting, high-fidelity simulation could fill the gap. This type of competency-based teaching and learning could assure that a fellow from any program would have a consistent, comparable, and meaningful experience in the specialized field of congenital cardiac anesthesia. The same would need to be developed for all learning areas within anesthesiology."

Learner assessment should be thought of in terms of formative and summative purposes. Formative assessment should be provided consistently throughout a fellowship program, as it provides trainees with feedback on their performance towards defined educational objectives. It also steers learning towards desired outcomes, and can focus high-achieving learners towards more rapid skill advancement. Summative assessment determines how well learners achieved competency of specific objectives at developmentally appropriate stages in their training. These are conducted at the end of a rotation or program.

For formative and summative learner assessment to be considered reliable, performance data must be obtained from the predominant clinical units where congenital cardiac anesthesia trainees work and learn. Multidisciplinary cardiothoracic team members, including supervising anesthesiologists, surgeons, nurses, and other staff members in the OR or ICUs, should use multiple assessment methods and tools (e.g., standardized checklists, performance audits, case logs), in combination with the trainee's own self-assessment, to create a comprehensive performance appraisal system required in a competency-based training model.

Learner assessment methods can be categorized as cognitive, affective, or psychomotor appraisals. Cognitive learner assessment methods are used to determine and provide feedback about trainees' acquisition and application of biomedical, clinical, epidemiological, and social behavioral sciences knowledge, as well as their ability to problem-solve, reason through clinical challenges, and use critical thinking skills. Methods include:

- Written or computer-interactive tests – multiple choice, essay-type questions
- Oral examinations
- Questionnaires
- Individual interviews
- Procedural, operative or case logs
- Chart stimulated recall
- Review of scholarly projects and research
- Observation of a fellow's ability to apply data from advanced monitoring devices.

Affective learner assessment methods are used to appraise and provided feedback about trainees' attitudes, feelings, motivations, and decisions. Methods include:

- Standardized patient exercises
- Questionnaires
- Written reflections and essays
- Rating and forced ranking forms
- Patient and family surveys
- Teamwork exercises
- Peer assessment of professionalism
- Case-based discussions that involve clinical uncertainty or ethical dilemmas
- Individual interviews
- Self-report of adverse events and near misses related to pediatric cardiothoracic and vascular anesthesia rotations
- Root cause analyses of medical errors or complications of patients under the fellows' care.

Psychomotor learner assessment methods are used to appraise and provide feedback on trainees' physical skills or the performance of actions. There are numerous methods to use for psychomotor assessment. Methods must be criterion-based, anchored using demonstrable behaviors, and developmentally appropriate. The most common methods are:

- Simulation exercises
- Portfolios of videotapes
- Direct observation of discrete procedural skills (such as intubation or line placement)
- Objective structured clinical examinations
- Objective structured assessment of technical skills
- Mini-clinical evaluation exercise
- Clinical encounter cards
- Clinical work sampling
- Practice metrics scoring using data collected as part of routine care via an existing perioperative information management system (e.g. central line insertion and temperature management).

The assessment process for congenital cardiac anesthesia trainees should emphasize learning, inspire confidence in the trainee, enhance the trainee's ability to self-monitor, and drive the institutions toward self-assessment and curricular change when necessary. The primary endpoint should be the ability to demonstrate trainee competence in the care of their patients in accordance with the ACGME's six core competencies – patient care, medical knowledge, systems-based practice, professionalism, interpersonal and communication skills, and practice-based learning and improvement.

In 2014, all anesthesiology residency programs will enter the ACGME's Next Accreditation System. A major aspect of this system involves the creation of roughly 30 milestones for each specialty that will map to different areas within the construct of the six core competencies. Milestones are "specialty specific achievements that residents are expected to demonstrate at established intervals as they progress through training" [38]. While it is not within the purview of this chapter to expound upon the anesthesiology residency milestones in detail, nor have milestones for anesthesiology specialty training been established, the reader is directed to the "The Anesthesiology Milestone Project," a joint initiative of the Accreditation Council for Graduate Medical Education and The American Board of Anesthesiology at http://www.acgme.org/acgmeweb/Portals/0/PDFs/Milestones/AnesthesiologyMilestones.pdf .

Program evaluation methods

Curriculum developers perform evaluation of an educational program to make judgments about its successes and deficiencies; decide about resource allocation, administrative support, and material management; determine teaching performance; uncover influencing attitudes regarding the curriculum's educational value; pinpoint

areas that are effective and that are in need of improvement; and conclude whether the curriculum met its intended learning goals and objectives and should continue to be incorporated into a training program.

A core component of the program evaluation process is to conduct and collect data from formative and summative learner assessment methods. The faculty must evaluate in a timely manner the fellows whom they supervise. In addition, the fellowship program must demonstrate that it has an effective mechanism for assessing fellow performance throughout the program and utilizes the results to improve fellow performance. At a minimum, faculty members responsible for teaching must provide critical assessment of the six ACGME core competences for each fellow at the end of 6 and 12 months of training. Learner assessment should include regular and timely performance feedback to fellows that includes at least semi-annual written evaluations. Such evaluations should be communicated to each fellow in a timely manner and be maintained in a record that is accessible to each fellow. The program director or designee must inform each fellow of the results of the evaluations at least every 6 months during training, advise the fellow of areas needing improvement, and document the communication. Assessments should include the fellows' fund of knowledge, clinical judgment and clinical psychomotor skills, patient management skills, and ability to critically analyze complex clinical situations. Periodic evaluation of patient safety and teamwork is mandatory. Evidence of the congenital cardiac anesthesiology fellows' scholarly projects and research, including those pertaining to continuous quality improvement and risk management, should be reviewed and summarized by designated faculty mentors.

The program director should conduct a final evaluation for each fellow who completes the program. This evaluation must include a review of the fellow's performance during the final period of education and should verify that the fellow has demonstrated sufficient professional ability to practice competently and independently. Documentation of the congenital cardiac anesthesiology fellows' successful completion of the program as well as subsequent training or career plans should be kept up-to-date, as this information will help to inform future program evaluation efforts. A program director should also maintain a listing of all graduating fellows' scholarly activities as well as aggregate feedback from the ACGME's Resident-Fellow Surveys. This survey provides feedback on duty hours, faculty supervision and instruction, fellow evaluation processes, educational content and resources, patient safety and teamwork, as well as overall reflections on the quality of the training program.

Faculty members

As part of a comprehensive curriculum evaluation effort, faculty members should be evaluated on their congenital cardiac anesthesia teaching performance and supervisory capabilities. Clinical teaching assessment instruments should produce valid and reliable results and any findings should be provided to faculty members in a clear and concise format. The faculty members should be assessed on their medical knowledge, clinical competence, teaching effectiveness, scholarly activities, and professional attributes. Lombarts et al. found that existing tools can be adapted for the systematic evaluation and support of faculty members involved in residency programs. They suggest basing faculty evaluation on qualities established by the well-known Stanford Faculty Development Program instrument. These qualities include establishment of an effective learning climate, professional attitudes towards trainees, communication of goals, evaluation of trainees, and quality of feedback provided. Moreover, Baker's study of resident assessment of educators in anesthesiology provides data about the positive impact that trainee evaluation can have in motivating clinicians to become better teachers [41].

Overall program effectiveness

Summative program evaluation provides information on the degree to which a curriculum has met its intended objectives and at what cost. It can also document the curriculum's success in engaging and motivating its learners and faculty as well as associated subspecialty anesthesiology training programs. In addition to quantitative data, summative program evaluation may include qualitative information about educational barriers and unanticipated obstacles as well as means to streamline curriculum implementation. The results of summative program evaluations are often disseminated to stakeholders to obtain or maintain time, administrative support, funding, and other resources. The educational effectiveness of a program must be evaluated at least annually in a systematic manner.

Representative program personnel (at a minimum the program director, representative faculty, and one fellow) must be organized annually to review program goals and objectives, and the effectiveness with which they are achieved. In the evaluation process, the group must take into consideration written comments from the faculty, the most recent report of the graduate medical education committee of the sponsoring institution, and the fellows' confidential written evaluations. If deficiencies are found, the group should prepare an explicit plan of action, which should be approved by the faculty and documented in the minutes of the meeting.

The program should use fellow performance and outcome assessment in its evaluation of the educational effectiveness of the fellowship program. Performance of program graduates in the certification examination should be used as one measure of evaluating program effectiveness. The program should maintain a process for using assessment results together with other program evaluation results to improve the fellowship program.

Curriculum maintenance and enhancement

Once a curriculum in congenital cardiac anesthesia has been developed, the next challenge is curriculum maintenance. A successful curriculum is continually developing by responding "to evaluation results and feedback, to changes in knowledge base and the material requiring mastery, to changes in resources (including faculty), to changes in its targeted learners, and to changes in institutional and societal values and needs". Areas for curricular enhancement may include review of the written or intended curriculum, assessment of the environment/setting of the curriculum, and determination of learner assessment methods to meet new accrediting agency requirements (such as the ACGME's milestones). The following data can be collected and utilized to assess how well a curriculum is functioning:

- Program evaluation
- Learner/faculty/patient questionnaires
- Patient quality metrics
- Objective measures of learners' skills and performance
- Focus group of learners, faculty, staff, and patients
- Other systematically collected data
- Regular/periodic meetings with learners and faculty
- Special retreats and strategic planning sessions
- Site visits
- Informal observation of curricular components, learners, faculty, and staff
- Informal discussions with learners, faculty, and staff

Congenital cardiac anesthesia is a subspecialty in which there are significant interactions between anesthesiologists and cardiac surgeons, cardiologists, radiologists, and other pediatric subspecialists. Close alliance between these disciplines is vital to the growth and development of the subspecialty. Furthermore, curriculum enrichment is dependent on both intra- and inter-subspecialty collaboration as well as combined faculty development efforts.

Dissemination

There is a need for an international comprehensive curriculum in congenital cardiac anesthesia. Local adaptation of a core curriculum will be necessary to overcome technological and cultural care delivery obstacles. The following issues should be considered when considering dissemination of core curriculum material:

- What material should be disseminated?
- How should the material be disseminated (publications, presentations, multi-institutional interest groups or academic societies, educational clearinghouses, online learning systems, digital communication, instructional videotapes or audiotapes, and/or instructional computer software)?
- What resources are required (time and effort, personnel, equipment/facilities, funds)?
- How can dissemination and impact be measured?

Dissemination of a curriculum can be a valuable process, benefiting many other congenital cardiac anesthesia trainees. A coherent strategy must be determined on what should be disseminated, appropriate methods of dissemination, and the best use of limited time and administrative resources.

Role of professional societies

At present, the CCAS, in conjunction with the Society of Pediatric Anesthesia (SPA), has taken the lead in developing a core curriculum for fellowship training in congenital cardiac anesthesia. Close future collaboration with the Society of Cardiovascular Anesthesiologists (SCA) will be necessary. The ACGME has revised the case requirements for the adult cardiothoracic anesthesiology fellowship in 2014 and has not mandated any case requirements at this time. Collaboration with the ACGME, RRC, and the American Board of Anesthesiology will be necessary as the subspecialty matures to the point where it becomes a board certifiable specialty in its own right. As many children with CHD survive to adulthood and develop adult cardiothoracic disease, the American Heart Association as well as the American College of Cardiology may be able to provide significant input into developing a holistic approach to the care of this complex patient population. A significant proportion will go on to become pregnant and hence both the American College of Obstetricians and the Society for Obstetric Anesthesia and Perinatology will need to contribute to the development of a curriculum.

Conclusion

Developing durable new curricula will be challenging in the highly specialized area of congenital cardiac anesthesia. Use of a systematic approach to its development will facilitate efficient teaching and learning in this complex discipline. It is important to develop programs that give faculty members the necessary skills to develop curricula and that provide mentoring. Finally, the challenge of transitioning trainees from fellow (learner) to faculty member (provider and teacher) in congenital cardiac anesthesia will be ongoing. Radical and creative changes in the existing method of instruction in congenital cardiac anesthesia are required to produce well trained additions to our profession. It is increasingly difficult to achieve, in a competitive clinical environment, clinical competency based on the traditional apprenticeship model, and hence the best method to achieve competency in our learners is yet to be determined. Trainees should be encouraged to create a learning portfolio, preferably web-based, that is a record of participation and achievement, career goals and professional development, physical evidence, and reflective writing.

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CHAPTER 3

Quality, Outcomes, and Databases in Congenital Cardiac Anesthesia

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Introduction

Patient safety in the operating room (OR) and beyond has long been a driving force in anesthesia care. Technical innovations such as pulse oximetry and capnography, combined with better trainee and practitioner education have dramatically increased safety for our patients and the quality of our anesthesia care. Additionally, newer medications, technologies and monitoring modalities continue to advance the field. As a result of these systematic changes, anesthesia-related patient morbidity and mortality have steadily declined across all patient populations. Non-technical attempts to reduce perioperative complications have become another major focus of various organizations such as the World Health Organization (WHO) and the Joint Commission for the Accreditation of Hospital Organizations (JCAHO). Efforts to delineate the frequency of complications related to anesthesia in patients undergoing congenital cardiac surgery and procedures in the cardiac catheterization laboratory and elsewhere have been difficult, because of the low occurrence of this surgery compared with other surgeries on children and the relatively rare incidence of anesthesia-related complications. Busy cardiac anesthesia services at major North American pediatric institutions will each only have contact with 2,000–3,000 congenital cardiac patients per year and the majority of these cases are non-surgical, such as diagnostic and therapeutic catheterizations and radiology procedures. The recognition of the need to systematically quantify and study outcomes in pediatric cardiac surgery, anesthesiology, and catheterization has led to several multi-institutional and multinational efforts to organize large databases over the past two decades.

This chapter begins with a discussion of errors and outcomes in surgery and anesthesia, emphasizing communication and teamwork. Next, systems for prospective risk assessment in pediatric cardiac surgery are discussed. Then, an analysis of closed malpractice claims in anesthesia is presented, and subsequently a discussion focusing on pediatric cardiac anesthesia morbidity and mortality. Finally, database initiatives in congenital cardiac anesthesia, surgery, and interventional catheterization are presented.

Errors and outcomes in surgery and anesthesia

The perioperative management of patients with congenital heart disease (CHD) is fraught and there are occasions when even small decision-making errors can have catastrophic outcomes. James Reason has described the "Swiss cheese model" for evaluating patient complications due to human errors [1]. For a complication to occur, all the "holes" in the cheese have to line up – that is, there is a sequential failure of various defense mechanisms in place

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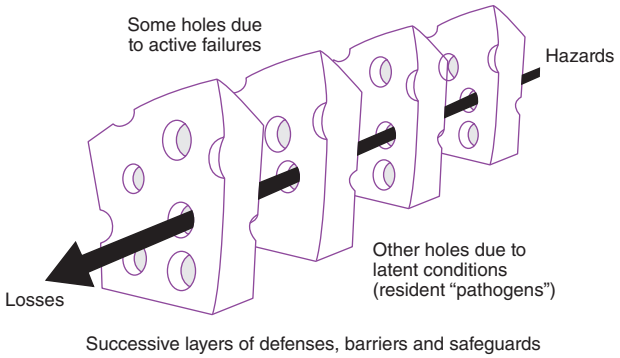

Figure 3.1 The "Swiss cheese" model of accident causation. Reproduced with permission of Cambridge University Press [1].

to prevent, recognize and/or treat unwanted physiologic changes (Figure 3.1). Many "anesthesia" complications are multifactorial in origin and it can be difficult to assign the relative contributions of different clinical services. For example, failure to successfully separate from cardiopulmonary bypass may be due to issues such as technical difficulty or bleeding (surgery), inotrope management (anesthesia and surgery), ventilator management (anesthesia), or underlying patient physiology such as intractable pulmonary hypertension. These system factors are further exacerbated if there are communication difficulties between the various parties, including surgeons, anesthesiologists, perfusionists, cardiologists, and the pre- and postoperative medical and nursing teams [2].

de Leval and colleagues investigated the impact of human factors and teams on surgical outcomes in congenital cardiac patients, focusing on the neonatal arterial switch operation (ASO) as a marker for complex, high-risk surgery [3]. Patient and procedural data were collected on 243 operations performed by 21 cardiac surgeons in the United Kingdom in 16 centers over 18 months. Of these 243 patients, case study data were collected on 173 ASOs by two human factors researchers who followed each case from the time of induction of anesthesia until care was transferred to the intensive care team. The observed adverse events were subsequently divided into major and minor events depending on their impact on the safety of the patient. Analyses determined that, after adjustment for patient factors, the total number of minor and major events per case were both strong predictors of the probability of death and near-miss events for major morbidity or death ($P < 0.001$). The authors concluded that minor events go largely unnoticed by the OR team and are therefore left uncompensated. A subsequent examination of the same data suggests that minor events impede the OR team's ability to compensate for future major events [4].

In addition to the organizational factors, pediatric cardiac surgery procedures have a low error tolerance. The Bristol Royal Infirmary Inquiry and the Manitoba Inquiry reports both recognized the importance of human factors and systems research in improving pediatric cardiac surgical outcomes [5,6]. The report of the Manitoba Pediatric Cardiac Surgery Inquest found that "serious organizational and personnel problems experienced by the Health Sciences Center's Pediatric Cardiac Surgery Program during 1993 and throughout 1994 contributed to the deaths of these children."

Galvan et al. published an observational study on complications in this complex patient population and recorded on average of 1.8 major compensated and nine minor compensated complications per case [7]. These complications were observed during the surgeries but were all recognized and treated by the medical team before injury resulted – all the "holes" in the Swiss cheese did not line up because one or more of the various systems in place to prevent patient injury worked appropriately. Barach et al. reported on a comprehensive process map in which they outlined the multiple steps involved in congenital cardiac anesthetic care and identified the potential sites for safety interventions [8]. They observed 108 open cardiac surgeries and found that communication failures were the most common underlying cause of major events. Examples of the organizational and human factors challenges that Barach et al. observed include:

- Unplanned transfusion of blood products correlated with a breakdown of communication between the anesthesia team, the nurses and the perfusionist.
- Failure to identify a non-functioning infusion pump was directly related to poor communication between the anesthesia attending physician and the resident who was performing several tasks simultaneously.
- Detection of increased chest tube bleeding was delayed and may have been related to suboptimal communication between residents and the attending physician.

"Near misses" are important as they are 10–100 times more common than documented adverse events and yet share the same organizational and cognitive sources of error as major adverse events. Determining the frequency and nature of "near miss" events is potentially far more important than just looking at system failures resulting in patient injury. However, "near miss" analysis is difficult as it requires a trained, independent observer to accompany the patient through the entire care continuum.

Outcome transparency has become a key component of programmatic evaluation. For example, news articles have disclosed congenital cardiac surgical program closures possibly related to adverse patient outcomes compared with their cohorts, while other institutions have made the decision to publicly release their pediatric heart surgery outcome data on a regular basis in an attempt to provide the most accurate data possible [9–11]. Although there is currently no mandatory reporting for congenital cardiac surgical or anesthesia programs nationwide, the Society of Thoracic Surgeons (STS) has begun providing "star" ratings on its website for adult heart surgery outcomes in isolated coronary artery bypass grafting or aortic valve replacement operations [12]. In Great Britain, congenital cardiac program mortality is reported publicly for all programs through the Central Cardiac Audit Database [13]. To date, there has been no similar effort to publish anesthesia morbidity and mortality, both because it is

so infrequent and because of the absence of a national clearinghouse.

KEY POINTS: ERRORS AND OUTCOMES IN SURGERY AND ANESTHESIA

- Reason's Swiss cheese model has been widely cited in explaining patient complications in complex systems.
- The total number of minor and major adverse events during complex congenital heart surgery were strong predictors of morbidity and mortality in de Leval's study.
- "Near-miss" events are 10–100 times more common than adverse events yet they share the same sources of error.

The six "Cs": communication and teamwork

In complex environments like pediatric cardiac ORs or catheterization laboratories, errors cannot and will not be avoided or eliminated. In his publication *Normal Accidents: Living With High-risk Technologies*, Perrow has postulated that even the best teams cannot eliminate every error [14]. What they can achieve at best is to prolong the time interval between errors. Therefore, it is of great importance for successful hospitals to create a culture of safety similar to the culture that the aviation industry promulgated to minimize the risk of human errors. More than a decade was required before hospitals were able to embed the concepts of checklists, team time-outs and sign in/sign out procedures as components of daily safety procedures. In commercial aviation, one must realize that computers in modern airplanes have taken over the human function of checking lists. These computers are checking the lists themselves automatically, because analysis of the human practice of using a checklist a hundred times reveals that this is a source of error in itself. The effort in the aviation industry now is more focused on team performance, simulation, and reducing errors due to hierarchy and authority issues. The six "Cs" – communication, cooperation, coordination, cognition (simulation and cross-training), conflict (managing disruptive behavior) and coaching (team-training) – are the key goals for successful working interdisciplinary teams. A comprehensive summary of this topic is presented by Wahr et al. [15].

The JCAHO and WHO have both advocated instituting a time-out system prior to procedures to minimize the risk of preventable complications such as wrong-site surgery and failure to administer antibiotics in a timely manner [16]. In addition, "closed-loop" communication has been encouraged to minimize system errors.(Figure 3.2) [17]. This particular technique is very helpful in the OR environment, where there can be a wide variety of distractions from background noise, cellular telephones, computers,

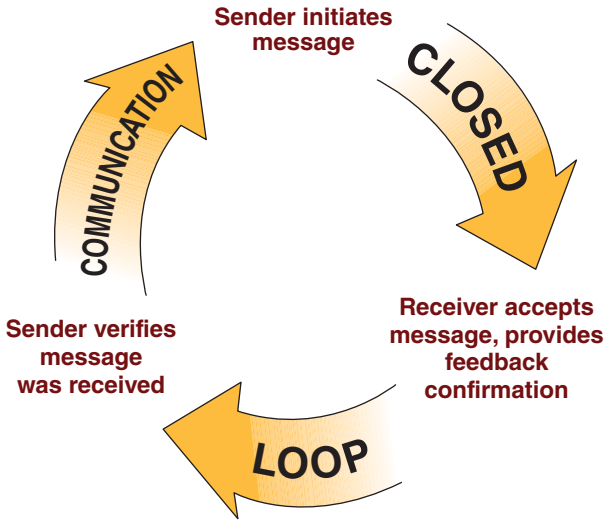

Figure 3.2 Closed-loop communication. (Source: Agency for Healthcare Research and Quality [17]).

monitors, conversations and alarms. Shaw and Stayer recently reviewed much of this literature in their chapter, "Operating room safety, communication and teamwork" in the most recent edition of *Gregory's Pediatric Anesthesia* [18]. There are a variety of additional techniques to maximize communication in the OR (or any other procedural location) as well as documenting the flow patterns that may lead to adverse events [16].

KEY POINTS: COMMUNICATION AND TEAMWORK

- Communication, cooperation, coordination, cognition, conflict management, and coaching are key goals for interdisciplinary teams.
- Checklists and timeout procedures are now accepted as mandatory components of complex systems such as congenital cardiac surgery.
- Closed-loop communication is an accepted strategy to minimize system errors.

Databases in pediatric cardiac surgery and anesthesiology

In order to better quantify both the incidence of adverse events and the outcomes of surgical procedures, in the 1990s the STS database committee established a nationwide (and now international) voluntary and anonymous registry of congenital cardiac cases and outcomes [19]. Of the 117 locations in the US and eight locations in Canada that provided surgical care for congenital cardiac lesions in 2013, the database had 112 centers submitting their information during the annual data harvest. This included almost every congenital cardiac center in the US (108 sites

out of 117) and four outside of the US (three in Canada and one in Japan). As of the Fall 2013 report, the STS Congenital Heart Surgery Database (STS-CHSD) held information on over 292,828 patient surgical procedures, more than half of which took place within the past 5 years. The European Association for Cardio-Thoracic Surgery (EACTS) has developed a transnational system for congenital cardiac surgery throughout the European continent and the UK. The EACTS utilizes a shared nomenclature for both lesions and complications with the STS that allows pooling of the two data sets to create an even larger picture of worldwide congenital cardiac surgery and outcomes.

These data serve as an important resource for determining nationwide outcomes on a given congenital cardiac lesion and benchmarks by which individual hospitals and surgeons can compare their results against aggregate results on a lesion-by-lesion, complexity, and age-adjusted basis. Both public and private payers have begun to incorporate these data in evaluating programs. The state of Florida, for example, has mandated participation in this type of database as a requirement for participation in state-run insurance programs such as Medicaid [20]. In New York state, the Department of Health publishes outcomes data on every program in the state, including whether they fall above or below 95% confidence intervals for expected outcomes after risk adjustment [21]. The private health insurer United Healthcare has established "centers of excellence" to facilitate referrals within their systems and to maximize their patient outcomes and satisfaction while minimizing the added expense of complications [22,23]. Demonstration of superior outcomes through benchmarking is one element of the requirements for consideration as a preferred referral center, and the popular US News and World Report Hospital and Specialty annual rankings include database participation and benchmarking in their ranking algorithm [24].

Other important efforts that have come out of the STS-CHSD include working groups that have established the consensus guidelines for defining lesion nomenclature, morbidity, and mortality [25]. All of these efforts have been coordinated internationally with other groups such as the EACTS to allow the free flow of comparative data across national boundaries. Additionally, work is ongoing to span specialties to involve pediatric cardiology, cardiac anesthesia, intensive care, and governmental agencies.

A well-recognized weakness of the current single-site reporting system is that a patient undergoing a procedure at one institution may suffer an adverse event that requires transfer to another institution. In the case of an adverse event, the latter facility becomes the center that reports the morbidity in their statistics, while the initial treating institution does not report the event. Efforts are underway to include incorporating state and national death indices to track patient mortality beyond the initial postoperative period and capture mortality information on patients lost to follow-up. Participant groups are also trying to develop US Health Insurance Portability and Accountability Act-compliant mechanisms for identifying individual patients as they move through their care at multiple institutions.

The Congenital Cardiac Anesthesia Society (CCAS) was incorporated in 2005 and one of its first initiatives was to approach the STS about developing anesthesia information to be included in the STS data set [26]. The STS has been very supportive of this collaboration and sees it as a model for future incorporation of additional specialties that share the same patients, such as pediatric interventional cardiology and pediatric cardiac critical care medicine. The CCAS work with the STS served as a model for the Society of Cardiovascular Anesthesiologists (SCA) Adult Cardiothoracic Anesthesia Database, which is now working in conjunction with the appropriate STS data set. The adult SCA database began entering patient data in 2013 and tends to focus more on echocardiographic findings rather than outcomes or adverse events [27].

A major benefit of utilizing an annual data submission process across multiple institutions is that it allows for a far more contemporaneous examination of patient outcomes. Publications from two centers with a long history of anesthesia data collection, the Boston Children's Hospital and the Mayo Clinic, illustrate the difficulties with single-center record-keeping [28,29]. Their data, critically important as it is, represents time periods ranging from 6 years (Boston) to 17 years (Mayo). During these time spans multiple factors may shift that significantly alter patient outcomes and potential complications. For example, personnel changes and experience (physician, nursing and ancillary staff), surgical technique modifications, pharmacology, technical advances with better monitoring and equipment, and more sophisticated complication detection and tracking all impact patient outcome statistics. In examining low-frequency events, the only way in which to properly determine their occurrence is to investigate large numbers of patients. As no single center can provide sufficient patients as a denominator in a short period of time, it is necessary to either lengthen the epoch studied (with the weaknesses mentioned earlier) or increase the denominator by expanding the patient base by making the data multi-institutional. One goal of the STS–CCAS collaboration is specifically to do the latter.

KEY POINTS: DATABASES IN PEDIATRIC CARDIAC SURGERY AND ANESTHESIOLOGY

- The STS Congenital Heart Surgery Database was the first multi-institutional effort to gather data on practice and outcomes.
- The EACTS has also developed a similar database for congenital heart surgery.
- Cardiac anesthesia databases have been initiated by the CCAS and the SCA, appended to the surgical databases.

Prospective risk assessment in pediatric cardiac surgery and cardiology

It is intuitive that different pediatric cardiac surgical procedures will have radically different long-term outcomes related to the underlying severity of the defect, the complexity of the operative repair, and the co-morbidities found in a given patient. In order to best estimate these potential outcomes, initial efforts were made at developing risk categories based upon "best guess" techniques in which groups of cardiac surgeons and cardiologists essentially sat down in a room and assigned each individual operative procedure to a risk category pool based upon their collective years of experience. The most widely adopted categorization schema utilizing this technique is the Risk Adjustment for Congenital Heart Surgery (RACHS-1) scoring system developed by Jenkins and colleagues [30,31]. The Aristotle Basic Complexity (ABC) score is another popular method of preoperative risk assessment utilizing expert consensus based upon values being assigned to three components: the potential for perioperative mortality, the potential for perioperative morbidity, and the technical difficulty of the proposed repair [32]. The ABC system expanded the number of procedures evaluated, as compared with the RACHS-1 system, but the RACHS-1 appears to better discriminate at predicting mortality when the two are compared against each other [33]. The weakness of both of these systems is that they are based upon a consensus estimation of experts in the field. The STS, in conjunction with the EACTS, subsequently developed a risk model developed from empirical outcome data from the two database groups, the Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery (STAT) mortality score. The STAT score was modeled utilizing over 70,000 records from the two societies and divides pediatric cardiac surgical procedures into five levels of mortality categories ("strata"); however, these are based upon the observed outcomes rather than *a priori* assignment by expert opinion and this process was then validated by comparison to a larger sample set of over 111,000 pediatric cardiac surgical cases in both the STS and EACTS registries [34]. Each mortality category was created so that the inter-category differences were sufficient to warrant assignment to either a lesser or a greater score category. Table 3.1 contains a listing of the STAT assigned procedures and their respective categories. The STAT, RACHS-1 and ABC scores are all based upon in-hospital mortality rates and do not fully account for either in-hospital morbidity or out-of-hospital mortality, such as inter-stage deaths that occur after discharge. Another major component that is not accounted for in these systems is morbidity, such as prematurity, genetic abnormalities, or co-existing diseases. Work is progressing on each of these issues as they relate to patient outcomes.

Pasquali et al. have drawn extensively from work done in adult cardiovascular surgery to determine the relevance of "failure to resuscitate" (FTR) as a marker for programmatic quality [35]. The authors start with the hypothesis that complications and morbidity will always occur in any complex system such as the surgical repair of congenital heart defects. A recent single-site retrospective analysis by Agarwal and colleagues found an incidence of identified adverse events of 43% (126 of 325 patients); this was in a retrospective chart review, not in the type of prospective observational study performed years earlier by de Laval and Barach, which might identify more subtle minor events that occur without being recorded [3,8,36]. What distinguishes high-performing programs from lesser-performing ones is not the incidence of adverse events *per se*, but the response to them.

Interventional cardiologists have also recently addressed predictive outcomes analysis. Bergersen et al. prospectively collected data from eight sites participating in the Congenital Cardiac Catheterization Project on Outcomes (C3PO) registry utilizing a web-based tool on all cardiac catheterization cases [37]. *Post hoc* analyses utilizing multivariate modeling then determined four discrete procedural risk categories based upon the age of the patient and the type of procedure being performed (diagnostic, valvuloplasty, device or coil closure, angioplasty, stent placement, stent redilation, and other). Adverse events were categorized on a scale of 1–5, with 1 being no adverse event noted, and 5 catastrophic (i.e., resulting in death or emergent surgical intervention to prevent death). The risk scoring method was called the Catheterization for Congenital Heart Disease Adjustment for Risk Method (CHARM). The purpose of the C3PO and CHARM project is to allow for appropriate risk adjustments to be made when comparing outcomes at a given center with expected outcomes. This is a critical part of the quality improvement process that must occur at every institution.

KEY POINTS: PROSPECTIVE RISK ASSESSMENT IN PEDIATRIC CARDIAC SURGERY AND CARDIOLOGY

- The RACHS-1 and ABC scores are two validated sytems to estimate risk of mortality according to surgical complexity.
- The STAT score is a new risk model developed from empiric outcome data and promises to be the most accurate method for estimating risk preoperatively.
- The CHARM project estimates the risk of adverse outcomes according to complexity of the interventional cardiac catheterization procedure.

Closed claims analysis in anesthesia

The American Society of Anesthesiologists has sponsored multiple investigations using a "closed claims" analysis method to identify areas of concern for anesthesiologists,

Table 3.1 Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery (STAT) Mortality Score Categories

Society of Thoracic Surgeons expected hospital discharge mortality rate (%, 95% confidence interval)*				
Mortality category 1 (0.55%, 0–1%)	**Mortality category 2 (1.7%, 1–2.2%)**	**Mortality category 3 (2.6%, 1.1–4.4%)**	**Mortality category 4 (8.0%, 6.3–11.1%)**	**Mortality category 5 (18.4%, 13.9–27.9%)**
ASD repair (patch)	PDA closure, surgical	Transplantation, lungs	Mitral valve replacement	DKS procedure
AVC repair, partial	PA, reconstruction main trunk	Occlusion MAPCAs	Pericardial drainage procedure	Transplantation, heart–lung
ASD + PAPVC	LV to aorta tunnel repair	Coarctation + VSD repair	Aortic arch repair	ccTGA, atrial switch, Rastelli
Aortic stenosis, subvalvular	Valvuloplasty, mitral	Konno procedure	Fontan revision or conversion	ccTGA, atrial switch, ASO
AICD implantation	Valvuloplasty, aortic	Coarctation, patch aortoplasty	DOLV repair	Norwood procedure
DCRV repair	1 1/2 ventricular repair	PA, reconstruction branch central	DORV, intraventricular tunnel	Truncus + IAA repair
ASD repair (primary)	Arrhythmia surgery, ventricular	Pulmonary artery aneurysm repair	Arterial switch + aortic arch repair	
VSD repair (patch)	Pacemaker, permanent	Right ventricular aneurysm repair	PA debanding	
Vascular ring repair	Ross procedure	VSD septal fenestration	ASO + VSD repair	
Coarctation repair, end–end	Glenn + PA reconstruction	Shunt, ligation and takedown	Cardiac tumor resection	
AICD procedure	Aortopexy	Hemi-Fontan	Transplantation, heart	
PFO, primary closure	Fontan, atriopulmonary	AVC repair, complete	Coronary artery bypass	
AVR, bioprosthetic	Bilateral bidirectional Glenn	Arterial switch operation	TOF – absent PV	
VSD repair (primary)	Aortic root replacement, mechanical	Valvuloplasty, truncal	Valve excision, tricuspid	
PVR	Conduit, LV to PA	Fontan, atrioventricular connection	Shunt, systemic to pulmonary	
Conduit reoperation	Coarctation, extended end-end	Pulmonary embolectomy, acute	TOF-AVC repair	
TOF, ventriculotomy, non-transannular	Anomalous origin coronary artery	ASD, partial closure	Ross–Konno	
Glenn, unidirectional	RVOT procedure	Rastelli operation	Senning	
AVC repair, intermediate	Aortic aneurysm repair	Conduit, ventricle to aorta	Ebstein's repair	
Coarctation repair, interposition graft	ccTGA, VSD closure	AVR, homograft	Aortic arch + VSD repair	
Fontan, TCPC, lateral tunnel, fenestrated	AP window repair	REV	PA banding	
Sinus of Valsalva repair	Valvuloplasty, pulmonic	Pulmonary artery sling repair	Aortic root replacement, homograft	
AVR, mechanical	TOF, ventriculotomy, transannular	Mustard	Unifocalization, MAPCAs	
	Aortic root replacement, bioprosthetic	Pulmonary atresia-VSD	Aortic dissection repair	
	Bidirectional Glenn	Conduit, RV to PA	ccTGA, VSD and LV to PA conduit	
	Aortic stenosis, supravalvular	Pulmonary embolectomy	Pulmonary atresia – VSD – MAPCA	

(*continued overleaf*)

Table 3.1 (*continued*)

Society of Thoracic Surgeons expected hospital discharge mortality rate (%, 95% confidence interval)*				
Mortality category 1 (0.55%, 0–1%)	**Mortality category 2 (1.7%, 1–2.2%)**	**Mortality category 3 (2.6%, 1.1–4.4%)**	**Mortality category 4 (8.0%, 6.3–11.1%)**	**Mortality category 5 (18.4%, 13.9–27.9%)**
	Pericardiectomy		VSD creation, enlargement	
	Conduit placement, other		HLHS biventricular repair	
	LV aneurysm repair		TAPVC repair	
	Fontan, TCPC, external fenestrated		Pulmonary venous stenosis repair	
	Pulmonary origin from ascending aorta		Shunt, systemic to pulmonary central	
	ASD, common atrium		Interrupted aortic arch repair	
	PAPVC, scimitar		ASO + VSD + aortic arch repair	
	Fontan, TCPC, external non-fenestrated		Truncus arteriosus repair	
	Pulmonary artery ligation		ASD creation/enlargement	
	Coronary artery ligation		Atrial septal fenestration	
	Aortic root replacement, valve sparing		Valve closure, tricuspid	
	Mitral stenosis, supravalvular ring			
	Arrhythmia surgery, atrial			
	Systemic venous stenosis repair			
	PA, reconstruction, branch peripheral			
	Valvuloplasty, tricuspid			
	TVR			
	Valve replacement, truncal			
	Fontan, TCPC, lateral tunnel non-fenestrated			
	Atrial fenestration closure			
	Cor triatrium repair			
	VSD, multiple			
	Atrial baffle procedure			
	Coarctation, subclavian flap			
	Partial LV reduction surgery			
	TOF, RV-PA conduit			

*Expected STAT score model-adjusted percent mortality before hospital discharge from surgical procedure, with 95% confidence interval (CI).

ASD, atrial septal defect; AVC, atrioventricular canal; PAPVC, partial anomalous pulmonary venous connection; AICD, automated internal cardiac defibrillator; DCRV, double-chambered right ventricle; VSD, ventricular septal defect; PFO, patent foramen ovale; AVR, aortic valve replacement; PVR, pulmonary valve replacement; TOF, tetralogy of Fallot; TCPC, total cavopulmonary connection; PDA, patent ductus arteriosus; PA, pulmonary artery; LV, left ventricle; RVOT, right ventricular outflow tract; ccTGA, congenitally corrected transposition of the great arteries; AP, aortopulmonary; TVR, tricuspid valve replacement; RV, right ventricle; MAPCAs, major aortopulmonary collateral arteries; REV, reparation a l'étage ventriculaire (REV procedure); DOLV, double outlet left ventricle; DORV, double outlet right ventricle; ASO, arterial switch operation; HLHS, hypoplastic left heart syndrome; TAPVC, total anomalous pulmonary venous connection; DKS, Damus–Kaye–Stansel; IAA, interrupted aortic arch.

Source: data are from O'Brien et al. [34].

including claims for death and brain injury, central venous line injuries, nerve injury, and airway injury [38–43]. These reports have not generally examined the effects of age or type of surgery and do not have a denominator that is needed to determine the incidence of injury. Jimenez et al. used the closed claims data to investigate pediatric anesthesia liability and segregated the data by type of surgery [44]. This report found that thoracic and cardiac surgeries accounted for slightly less than 10% of all claims that were settled. This figure probably represents a disproportionately high number because of the relative paucity of thoracic and cardiac surgeries compared with all surgeries performed on pediatric patients. Malpractice data are a very insensitive tool for determining the incidence or causality of complications, as so many different factors apart from medical error determine whether or not a claim is initiated or settled. The denominator of pediatric patients undergoing surgical and diagnostic procedures with anesthesia in the United States is not measurable with any accuracy due to the lack of a central reporting mechanism. Examining the caseload at children's hospitals is insufficient because many procedures are performed in mixed adult–pediatric general hospitals, ambulatory surgical centers, or physicians' offices. Furthermore, there are well-known weaknesses to using the closed claims data. These analyses rely upon the presence of a settled malpractice claim to be included and the period examined may span decades during which significant changes in anesthesia, medical, and surgical practice have occurred.

Pediatric and congenital cardiac anesthesia morbidity and mortality

Over the last decade, a number of manuscripts concerning cardiac arrest in children have been published, some of which focused on children with CHD, with others focusing on children undergoing all types of surgical and non-surgical procedures [28,29,45,46]. The Pediatric Perioperative Cardiac Arrest (POCA) Registry was a multi-institutional effort in which participants anonymously reported all episodes of cardiac arrest in children aged 18 and younger that resulted in chest compressions or death at the time of surgery or within 24 hours. This project was begun in 1994 and data collection and analysis continued through 2004, at which time further data collection was put on hold. Subsequent examination of the detailed data forms allowed the investigators to assess the relative contribution of anesthesia to the cardiac arrest or death. The most recent publication from the POCA group was a follow-up to their original publication in 2000, and focused the analysis on arrests in patients with heart disease [47,48]. The authors reported that cardiac arrests in these patients were more likely to be in unrepaired patients (59%) or palliated patients (26%) than in patients with repaired cardiac lesions (15%). In 2010, Ramamoorthy et al. re-examined the POCA data, specifically assessing children with congenital heart defects [49]. Overall, they found that of the 373 anesthesia-related cardiac arrests, 127 (34%) patients had congenital or acquired heart disease – a number, not surprisingly, far out of proportion to the incidence of heart disease in the pediatric population (0.8%). Patients with single ventricle physiology were those most likely to suffer a cardiac arrest, while those with aortic stenosis and cardiomyopathy were associated with the highest mortality rates.

Building on the scope of the POCA registry, the Wake Up Safe (WUS) Database is, at the time of writing, a voluntary registry of 19 pediatric hospitals in the US, organized to record serious adverse events during the perioperative period [50]. The aim of this project is not only to collect data on cardiac arrest events like POCA, but also to continuously collect data on adverse events or "near misses," such as acute lung injury, musculoskeletal injury, spinal cord injury, or surgery on the wrong patient/site. An initiative started by the Society for Pediatric Anesthesia (SPA) in 2009, WUS hopes to provide ongoing monitoring of these very rare events across multiple institutions, and to use these data to uncover ways to prevent them from recurring. Because of the way in which the WUS initiative is structured, it will be possible to determine the incidence of these events and not just record their existence. It is, however, limited at this time to only a relatively small number of major pediatric centers and does not encompass many locations outside of these centers where the majority of pediatric cases occur such as ambulatory surgery centers, private offices (such as dental operatories), and general community hospitals.

Since the WUS project began, statements have been published on their website concerning hyperkalemia, preventing wrong site procedures, and decreasing the risks of intravenous medication errors. A recently published paper reported the first WUS database analysis: of 736,365 pediatric anesthetics of all subspecialties in the database there was a serious adverse event rate of 1.4/1,000 anesthetics, with respiratory events most common (254 of 740) and cardiac arrest the next most frequent (241) [51].

The investigators at Boston Children's Hospital have been collecting anesthetic data on their own patients since January 2000, both for internal quality and for state reporting requirements in Massachusetts. The publication of this data through December 31, 2005 from their cardiac ORs represents a significant effort to determine contemporary complications specific to pediatric cardiac anesthesia-related morbidity [28]. One of the difficulties associated with determining causality in this patient population is the interdependent nature of anesthesia, surgery, and patient physiology. The authors examined each incident with a panel of three pediatric cardiac anesthesiologists, with a subsequent review by a pediatric cardiac surgeon, before assigning causality. Boston Children's Hospital reported that in their series of 5,213 cardiac surgical patients from 2000 to 2005, there were 41 cardiac arrests in 40 patients for an overall frequency of 0.79%, with anesthesia playing a significant role in 11 of the 41 cases, or, in other words, 21.1 cardiac arrests per

10,000 anesthetics. This compares with their previously reported anesthesia-related incidence of 2.7 cardiac arrests or death per 10,000 anesthetics in all pediatric patients during roughly the same time period [52].

In 2013, the investigators from Boston Children's Hospital again reviewed their institutional databases to examine the incidence of cardiac arrest in children with CHD undergoing cardiac catheterization and describe potential risk factors for anesthesia [45]. In total, 7,289 catheterization procedures were performed between January 1, 2004 and December 31, 2009, and were classified as either a biopsy (19%), diagnostic (23%), or interventional catheterization (58%) [45]. Seventy procedures were associated with a cardiac arrest, with a reported frequency of 0.96/100 cardiac catheterizations. The authors acknowledge that although the frequency of arrest is higher than other multi-institutional reports, it is comparable to the results of their prior study on the incidence of arrest in the cardiac OR. The incidence of cardiac arrest in the population studied was found to be statistically significantly higher for children undergoing interventional procedures and those who were younger at the time of the procedure ($P < 0.001$). These authors concluded that these high-risk patients should be managed by an anesthetic team familiar with the pathophysiology, cases, environment, and perioperative staff, in order to facilitate communication and prompt resuscitation should the need arise. There also appeared to be an overall decline in the incidence of cardiac arrest when sedation and anesthesia were provided more routinely by a dedicated pediatric cardiovascular anesthesia team in the latter half of the data collection period.

Another institution with a long history of anesthesia data collection, the Mayo Clinic in Rochester, MN, also reviewed their experience with cardiac arrests in children [29]. A consistent factor in all of these studies is that children with underlying congenital cardiac defects are at a much higher risk of cardiac arrest than children without these defects. The incidence of cardiac arrest at the Mayo Clinic for children during non-cardiac procedures was 2.9/10,000, as compared with 127/10,000 for children undergoing cardiac procedures, a 30-fold increase in risk. Sub-analysis related to causality, age, and type of surgery further stratified their data. Of their 92,881 patients, 4,242 were for cardiac procedures. Within the 54 children who suffered a cardiac arrest or death undergoing a cardiac procedure, age played a significant role, with neonates having the highest risk. Anesthesia was not identified as a causative factor in any of the cardiac surgical arrests or death. At the Royal Children's Hospital, Melbourne, Australia, van der Griend and colleagues examined anesthesia-related mortality in 101,885 anesthetics administered to 56,263 children from January 1, 2003 through August, 2008 [46]. They, too, utilized an expert review panel of three senior anesthesiologists, examining the record of every patient who died during this time period who had received an anesthetic in the preceding 30 days. Overall anesthesia-related mortality was found to be 1 in 10,188 cases (0.98/10,000). All 10 deaths where anesthesia was found to be a contributing factor had significant pre-existing conditions, with pulmonary hypertension present in 50%. There were no anesthetic-related morbidities in children without underlying medical problems. Overall mortality was significantly higher in children < 30 days old and those with cardiac disease (particularly after 30 days of life).

As is evident from the most recent data, even the busiest of programs only infrequently have anesthesia-related cardiac arrests or death, because of the low incidence of these events. As a consequence, it is necessary to harvest data over many years to collect any meaningful numbers, during which time major changes in patient management may occur. For example, the initial POCA study attributed many arrests to the use of the anesthetic agent halothane, a known cardiac depressant [48]. By the time of the follow-up publication 7 years later, halothane had been replaced almost entirely in North America by sevoflurane, an anesthetic agent with significantly less cardiotoxicity at the typically administered doses.

KEY POINTS: PEDIATRIC AND CONGENITAL CARDIAC ANESTHESIA MORBIDITY AND MORTALITY

- The POCA Registry reported that 34% of cardiac arrests under anesthesia had heart disease as a factor.
- The Boston Children's Hospital registry has reported a cardiac arrest rate of 0.79% for cardiac surgery, and 0.96% for cardiac catheterization.
- The Mayo Clinic study reported a 30-fold increase in risk of cardiac arrest with cardiac surgery vs. non-cardiac surgery in pediatric patients.
- The Royal Children's Hospital study reported that pulmonary hypertension was a factor in 50% of anesthesia-related deaths.

CCAS and the Congenital Cardiac Anesthesia Network (CCAN)

The Congenital Cardiac Anesthesia Society was formed in 2005 by representatives from many of the busiest congenital cardiac surgical programs in North America. It is a subsidiary of the SPA and its work is closely coordinated with that organization. Membership is open to all individuals providing anesthesia-related care for children with heart defects or an interest in the field and it currently has almost 700 members both from the US and internationally. In addition to educational programs at its conferences and as a sponsor of other educational efforts, a major function of the organization is the development of a data registry linked to the STS-CHSD. In the UK and Ireland, CCAN is an informal organization of pediatric cardiac anesthetists numbering 70–80 physicians, which sponsors

an annual meeting for presentation of timely topics and discussion/debate about clinical practices. CCAN also sponsors a mailing list for regular updates.

Joint CCAS–STS database initiative

The Joint CCAS-STS Congenital Cardiac Anesthesia Database is a collaborative project developed over the last decade by multiple parties interested in capturing anesthesia-related information on these high-risk patients. The process by which this project came about is described elsewhere [8]. Anesthesia-related data fields for the database are selected by a database committee of the CCAS in coordination with the existing fields in the STS-CHSD. For an additional fee, STS-CHSD participating centers may elect to submit their anesthetic data to be pooled anonymously with the other participating centers during their annual data harvest. Importantly, the anesthesia data set includes information on congenital cardiac patients undergoing procedures outside of the cardiac ORs, including cardiac catheterization and non-cardiac surgical procedures. As noted previously, these patients represent a particularly high-risk subset of the pediatric population.

The interdependent relationship between congenital cardiac surgery and congenital cardiac anesthesia supports the creation of a common database for these subspecialties. Multiple potential benefits are being realized through the development of this joint database:

- Minimization of data entry burden
- Minimization of costs associated with data entry
- Minimization of the cost associated with database maintenance
- Utilization of common nomenclature based on The International Pediatric and Congenital Cardiac Code [53].
- Utilization of common database fields
- Utilization of common database definitions
- Utilization of common database standards
- Development of common strategies to report outcomes
- Development of common quality improvement initiatives.

The Joint CCAS-STS Congenital Cardiac Anesthesia Database began collecting data in January 2010. The data is harvested semi-annually. As of the Fall 2013 harvest, over 41,000 distinct anesthesia records have been analyzed from 35 programs in the US. These anesthesia centers represent a large cross-section both geographically and in terms of volume. Surgical cases represent 66% of the caseload while cardiology cases account for 18%, and "other" cases (thoracic, non-cardiac/non-thoracic procedures on cardiac patients) represent the remaining 16%.

Adverse events were reported overall in 790 of the 40,218 (1.9%) cases. The most common adverse event reported (other than difficulty obtaining vascular access within 1 hour) was unanticipated difficulty with intubation (145 incidents, 0.4%). Cardiac arrest unrelated to surgical or procedural manipulations occurred 76 (0.2%) times. The STS-CHSD, including the anesthesia component, is updated approximately every 3 years. The most recent update became active on January 1, 2014. The CCAS Database Committee has made several modifications to the data being collected, including multiple additions to the adverse outcome reporting options. The committee also worked with the STS to consolidate and clarify duplication of data entry items, such as blood transfusion categories, and added additional medication and blood product categories to reflect newer pharmacologic options. The complete data collection forms are available on the STS website, as is information about how to become a participating center [54]. Table 3.2 lists the adverse events being collected by the CCAS–STS-CHSD.

International efforts

Efforts are ongoing to make this database initiative a global project. Initial collaborative discussions have taken place about the possibility of linking this initiative with the European Association of Cardiothoracic Anaesthesiologists [55]. The final selection of database fields will be made through a collaborative effort involving surgeons and cardiologists from Europe and North America, as well as other continents. It is certainly possible and desirable that the STS-CHSD has an identical anesthesia module in the congenital heart database of EACTS and The European Congenital Heart Surgeons Association. These European and North American congenital heart surgery databases have functioned as sister databases with identical nomenclature and database fields and definitions [56,57]. The incorporation of anesthetic data into the effort should follow a similar strategy. This project should also ideally spread beyond North America and Europe. Efforts to involve Africa, Asia, Australia, and South America are necessary and already underway, under the leadership of The World Society for Pediatric and Congenital Heart Surgery [58].

The creation of a joint cardiac surgery and anesthesia database is another step towards the ultimate goal of creating a database for CHD that spans both geographic and subspecialty boundaries and can potentially capture a patient's lifetime of cardiac care regardless of their location. The Pediatric Heart Network, a research consortium of major congenital cardiac centers, has recognized this need and is supporting the creation of linkage between various registries such as the CCAS, STS, EACTS, Congenital Heart Surgeons' Society, the ACC IMPACT Interventional Cardiology registry, and the Pediatric Cardiac Critical Care Consortium (PC^4) ICU registry, as well as others [59].

Measuring outcomes has become a critical component of all facets of medical practice today. It is important for anesthesia and, in particular, for practitioners of pediatric cardiac anesthesia because of the extremely high-risk nature of this practice. Regular review of both caseload and outcomes in a structured manner through quality improvement conferences, mortality and morbidity, and

Table 3.2 Congenital Cardiac Anesthesia Society–Society of Thoracic Surgeons Database Adverse Event Fields (as of January 1, 2014)

Event	Definition
None	No anesthesia-related adverse events noted in the perioperative period
Airway – respiratory events	
Oral/nasal injury – bleeding	Bleeding noted in oropharynx or epistaxis, dental, lip or nasal injury
Respiratory arrest	Need to intervene in airway management in unplanned way (i.e., converting from cannula to ETT or LMA to ETT)
Laryngospasm requiring medication	Laryngospasm requiring medical intervention other than positive pressure
Difficult intubation/reintubation	Unplanned difficult intubation or reintubation
Bronchospasm	Wheezing requiring medical intervention other than suctioning
Hemoptysis/pulmonary hemorrhage	Bleeding either from endotracheal tube or postoperative hemoptysis
Stridor/subglottic stenosis	New-onset stridor noted after extubation requiring intervention
Extubation	Unplanned extubation (except if TEE-related – see below)
Endotracheal tube migration	Endotracheal tube needing to be repositioned in ICU on arrival chest X-ray
airway injury	Barotrauma/pneumothorax secondary to positive pressure ventilation
Pulmonary hypertensive crisis	Probable or definite PH crisis requiring intervention
Unplanned need to remain intubated due to anesthesia	Need to remain intubated at conclusion of procedure due to anesthesia factors (oversedation, muscle relaxation)
Hypercyanotic episode ("tet" spell)	Hypercyanotic episode (decrease in SpO_2 > 20% from baseline) requiring intervention other than establishing airway ("Tet" spell)
Vascular access events	
Arrhythmia – CVL placement	Arrhythmia therapy needed other than withdrawing wire or catheter
Myocardial injury – CVL placement	Myocardial perforation
Vascular compromise – CVL placement	Extremity ischemia or compromise with CVL placement
Pneumothorax – CVL placement	Pneumothorax during placement of CVL
Vascular access	Inability to obtain desired vascular access within 1 hour of induction anesthesia (PIV/Aline/CVL)
Hematoma requiring relocation of catheter	Significant hematoma that requires changing site of desired access
Arterial puncture	Inadvertent arterial puncture during CVL placement
Intravenous/intra-arterial air embolism	Air embolism causing hemodynamic change or ischemia
Arterial line placement – extremity ischemia	Extremity ischemia or compromise with arterial line placement
Intravenous Infiltration	Peripheral or central IV infiltration
Regional anesthetic events	
Bleeding – regional anesthetic site	Bleeding at site of regional anesthetic placement
Intrathecal puncture – regional	Inadvertent intrathecal puncture during caudal or epidural placement
Local anesthetic toxicity – regional	Systemic evidence of local anesthesia toxicity (ECG changes, CNS changes)
Neurologic injury – regional	Injury to peripheral nerve during regional nerve block
Drug-related events	
Anaphylaxis/anaphylactoid reaction	Suspected anaphylactic/anaphylactoid reaction requiring intervention for either hemodynamic support or respiratory intervention
Non-allergic drug reaction	Non-anaphylactic reaction such as "red man" syndrome or hypotension
Medication administration	Wrong medication administered
Medication dosage	Wrong dosage of correct medication
Intraoperative recall	Recall of intraoperative events
Malignant hyperthermia	Suspected or confirmed malignant hyperthermia reaction requiring dantrolene
Protamine reaction	Significant reaction to protamine requiring intervention other than slowing administration
Cardiac arrest events	
Cardiac arrest – anesthesia-related	Cardiac arrest requiring CPR during anesthesia care not related to surgical or catheter manipulation
Cardiac arrest – not anesthesia-related	Cardiac arrest requiring CPR during surgical or catheter manipulation
TEE-related events	
TEE-related esophageal bleeding/injury	TEE-related esophageal bleeding noted during or after TEE removal
Esophageal chemical burn	TEE-related injury to esophageal mucosa due to TEE cleaning chemicals
TEE-related airway compromise	TEE-related compromise of ventilation or oxygenation requiring removal of TEE
TEE-related extubation	TEE-related inadvertent extubation of patient

Table 3.3 (*continued*)

Event	Definition
Other anesthetic care events	
Complications during patient transfer	Any event occurring during movement of patient into/out of procedure, such as loss of IV or arterial line, airway compromise, disconnection of lines
Peripheral nerve injury due to positioning	Temporary or permanent nerve injury noted postoperatively due to positioning during procedure
Integument injury under anesthesia	Skin breakdown or dehiscence or alopecia noted postoperatively due to positioning during procedure
Ocular injury (corneal abrasion or injury)	Ocular injury noted postoperatively, such as corneal abrasion
Post-anesthetic events	
Postoperative nausea/vomiting	PONV requiring unplanned admission
Emergence delirium requiring medication	Emergence agitation or delirium requiring medication
Anesthetic equipment/other events	
Anesthesia equipment malfunction/failure	Any anesthesia equipment malfunction or failure during procedure
Other	Any event related to anesthesia care not otherwise listed

ETT, endotracheal tube; LMA, laryngeal mask airway; TEE, transesophageal echocardiography; ICU, intensive care unit; PH, pulmonary hypertension; SpO_2, pulse oximeter oxygen saturation; tet, tetralogy of Fallot; CVL, central venous line; PIV, peripheral intravenous catheter; Aline, arterial line; ECG, electrocardiogram; CNS, central nervous system; CPR, cardiopulmonary resuscitation; PONV, post-operative nausea/vomiting.
Source: data fields are from Vener et al. [26].

individual case reviews can help to educate anesthesia departments and individuals and perhaps minimize future adverse outcomes. Open lines of communication with our surgeons, cardiologists, and intensive care physicians are a key component of this process, along with the recognition that adverse events are inevitable in such a system and our job is to always be vigilant and ready to act on the patient's behalf.

KEY POINTS: NETWORKS AND DATABASES

- A major database effort has been initiated by CCAS in conjuction with the STS Congenital Heart Surgery Database.
- Both cardiac surgical and non-cardiac surgical anesthetics can be entered, and as of 2013, 41,000 anesthetics from 35 US programs have been analyzed.

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http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 4

Development of the Cardiovascular System and Nomenclature for Congenital Heart Disease*

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Introduction

Congenital heart disease (CHD) is the most common birth defect, occurring in 0.8% of live births and accounting for almost one-third of all major congenital anomalies [1,2]. The etiology and mechanisms of congenital cardiac malformations are not yet fully understood, and much of our understanding is derived from vertebrate animal models and progress in genomics, proteomics, transgenesis, imaging, and integrative systems biology [3]. Although cardiac anomalies are sometimes considered to have genetic and non-genetic causes, the multifactorial inheritance of some lesions is probably due to the interactions between several genes and modulating environmental factors, including known teratogens (such as alcohol, isotretinoin, and anticonvulsants), infectious agents (such as rubella), or maternal disease (such as diabetes mellitus and obesity) [4,5]. Developmental mechanisms include genetic and epigenetic molecular events, signaling, cell migration, and hemodynamic and contractile forces [6]. Analyses of the signaling pathways and regulatory factors that affect cardiac morphogenesis have begun to explain what causes specific cell lineages to commit to certain regions of the heart and how cardiac development is guided by decisions regarding cell migration, differentiation, proliferation, and death [4,7–9]. Furthermore, it has recently been recognized that the genes and developmental mechanisms producing CHD also play a role in the pathogenesis of cardiac dysfunction in adults with CHD [8,10]. Determining the cell lineages in the embryo has provided an insight into adult lineages and has opened the door for using regenerative medicine and novel therapies to treat congenital and acquired heart disease. It must be stated that much of the knowledge and understanding we have regarding cardiovascular development was derived from research in non-human species, which was performed with the hope that the same processes occur in humans. For detailed foundational information on the cell biology of cardiac development, the reader is referred to two excellent textbooks, *Cardiac Development* by Margaret Kirby [11], which is cited frequently in this chapter, and *Heart Development and Regeneration*, edited by Nadia Rosenthal and Richard Harvey [3].

This chapter consists of two different but somewhat interrelated parts. The first part of the chapter uses an anatomical approach to describe the development of the heart and vascular system and demonstrates the relationships between abnormal development and specific congenital cardiac anomalies. Although a segmental approach is used to describe embryology, cardiovascular

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development is a three-dimensional, spatiotemporal process with many elements occurring simultaneously. The second part of this chapter discusses the nomenclature for CHD, the sequential segmental approach to CHD diagnosis, and the morphologic evaluation of the congenitally malformed heart. These subjects represent the mainstay of pediatric cardiology practice and CHD diagnosis.

In view of the different emphasis of the two parts of this chapter, the authors have approached them as stand-alone topics for all practical purposes, in order to facilitate the ability of the reader to explore one or the other subject independently, if so desired.

Development of the cardiovascular system

New concept of cardiac development

Up until the 1990s, the conventional view of cardiac development was based on the *segmental model*, in which the primordiums of all the future components of the heart were hypothesized to be present in the initial heart tube [12]. Many of the classic concepts have been challenged over the past two decades as advancements have been made in labeling and transgenic fate-mapping techniques. Although the labeling studies performed by Stalsberg, de la Cruz, and Viragh from 1969 onwards suggested that cells were added to the poles of the heart from the surrounding mesoderm [13–15], more recent research conducted by Buckingham, Markwald, and others in the chicken and mouse have confirmed that cells are added to the heart after the initial stage of looping [16–18]. As discussed in detail in the following, it is now thought that the primitive heart tube contains little more than the precursors for the left ventricle and that the precursor cells of the other cardiac components are added to both the venous and arterial poles from a second heart field outside the initial heart tube [12]. Elucidation of the genetic and transcriptional networks regulating cardiac development has provided new insight and has increased our understanding of congenital cardiac malformations.

Cardiovascular development: normal and abnormal

The human embryo has no heart or vascular system during the first 2 weeks of life. Instead, it relies on diffusion from the utero-placental circulation. At the end of the second week, the embryo is a bilaminar disc made up of the epiblast and the hypoblast. In vertebrates, the cardiovascular system is the first organ system to develop and function; this begins during the third week of life when diffusion is no longer adequate to meet the nutritional requirements of the embryo. The embryo develops into a trilaminar disc by the process of gastrulation, thereby establishing all three germ layers – the ectoderm, mesoderm, and endoderm. Gastrulation involves cells in the epiblast migrating through the primitive streak caudal to the primitive node. These cells detach from the epiblast (invagination), and some displace the hypoblast to create the embryonic endoderm, others come to lie between the epiblast and endoderm to form the mesoderm, and the remaining epiblast cells form the ectoderm (Figure 4.1) [19]. The epiblast is, therefore, the source of the ectoderm, mesoderm, and endoderm.

Cardiogenic fields

Cardiac progenitor cells are located in the epiblast, just lateral to the primitive streak. After gastrulation, these cells migrate laterally and cranially to the lateral plate mesoderm. The lateral plate mesoderm becomes split by the pericardial coelom into the somatic (dorsal) and splanchnic (ventral) layers (Figure 4.2). Cells in the somatic layer will form the pericardium, and cells located in the bilateral *cardiogenic* or *heart fields* in the splanchnic layer will form the myocardium [20]. The heart fields merge in the midline, cranial to the stomatopharyngeal membrane, to form the *cardiac crescent* (Figure 4.3A,B). There are at least two distinct lineages of cells within the cardiac crescent: one population is referred to as the "first heart field" (FHF), and the other is referred to as the "second heart field" (SHF) [7]. The SHF is contiguous with and located dorsal and medial to the FHF. The FHF will give rise to

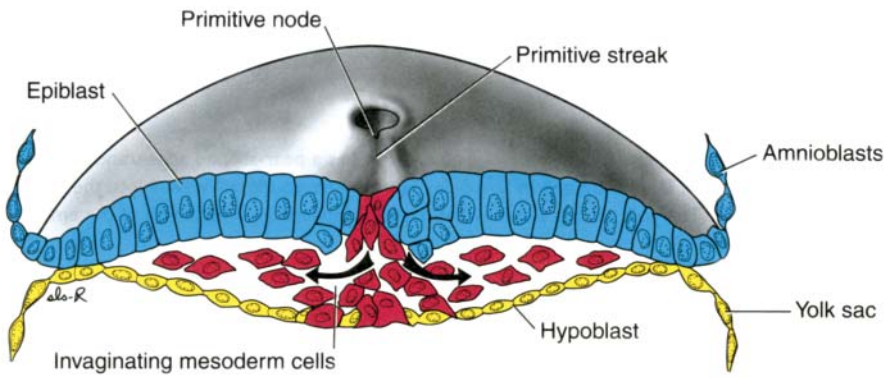


Figure 4.1 Formation of three cell layers. Cross-section through the primitive streak of the embryonic disc showing invagination of epiblast cells with displacement of the hypoblast to create the definitive endoderm and formation of mesoderm. (Source: Sadler [19]. Reproduced with permission of Lippincott Williams & Wilkins.)

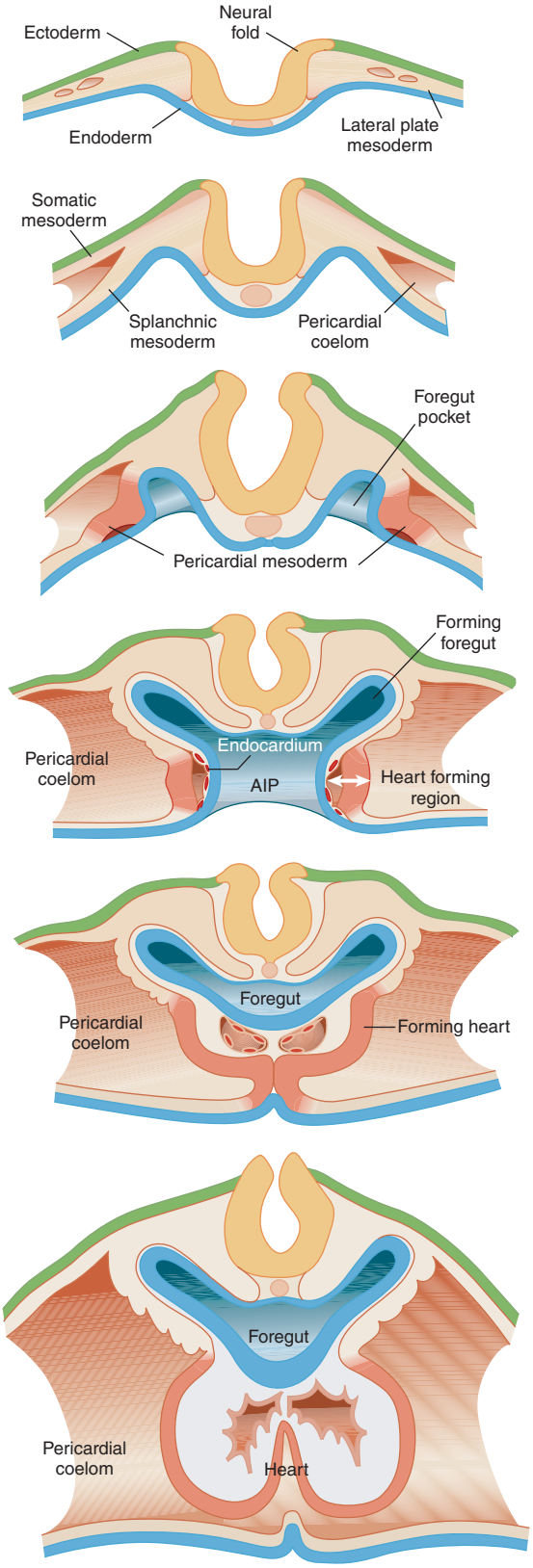


Figure 4.2 Diagrammatic representation of the formation of the heart, foregut pocket, and coelom in the chick embryo. AIP, anterior intestinal portal (Source: Kirby [11]. Reproduced with permission of Oxford University Press.)

the linear heart tube, and cells from the SHF will be added at the inflow (venous) and outflow (arterial) poles during cardiac looping. Differentiation of the heart field cells into myocardium is dependent on signals from the adjacent endoderm, and the proliferation and differentiation of SHF cells is delayed relative to that of the FHF cells [21]. As discussed in the following, the embryonic cells that contribute to cardiac development arise not only from the heart field mesoderm but also from cardiac neural crest [22] and the proepicardium [23].

KEY POINTS: CARDIOGENIC FIELDS

- Myocardial cells are derived from the bilateral cardiogenic or heart fields in the splanchnic layer of the lateral plate mesoderm.
- The heart fields merge to create a cardiac crescent, giving rise to two lineages of cells referred to as the first and second heart fields.
- Cells that contribute to cardiac development originate from heart field mesoderm, cardiac neural crest, and the proepicardium.

Formation of the heart tube

The primitive linear heart tube is formed during the fourth week of development from the FHF cells with the folding of the embryo. Contrary to originally held beliefs, the cardiogenic fields do not fuse cranially to caudally in a zipper-like fashion. Folding of the embryo brings the lateral portions of the cardiac crescent together to form the ventral part of the heart tube [24] (Figure 4.3C–G). The medial portions of the cardiac crescent will form the dorsal part of the heart tube, which is suspended from the foregut by the dorsal mesocardium. The heart tube has two caudolateral inlets (venous pole) and one craniomedial outlet (arterial pole) [24,25]. After folding of the embryo, the SHF mesoderm is located in the dorsal pericardial wall. The schematic drawings in embryology textbooks illustrating the presence of all the cardiac segments in the straight heart tube prior to looping are hypothetical constructions, as most of the segments are added to the primitive heart tube during the looping stages [26].

The myocardium of the heart tube is called primitive or primary because, unlike adult working myocytes, the myocytes of the heart tube have few contractile elements, a poorly developed sarcoplasmic reticulum, a low density of gap junctions, and high automaticity [12]. The endocardium is composed of a specialized endothelial cell type that is also derived from the splanchnic mesoderm and develops simultaneously with the myocardium in the cardiac crescent. A distinct population of mesodermal cells in each heart field undergoes *de novo* vasculogenesis into two hollow endocardial tubes that join to form a single tube. The endocardium becomes contiguous with the endothelium of the developing vasculature. The cardiac jelly, a thick acellular matrix secreted by the myocardium,

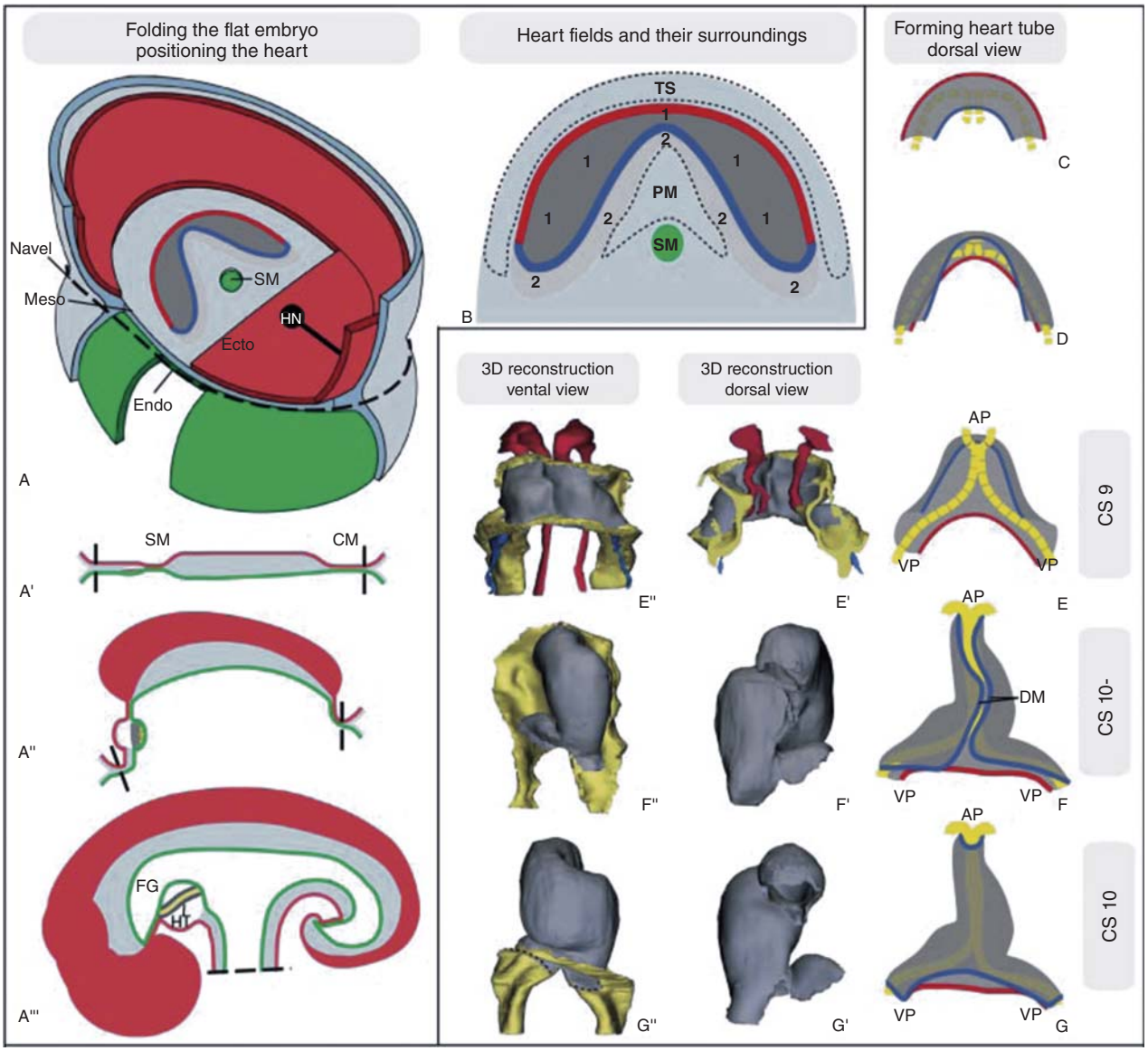


Figure 4.3 Folding of the embryo and formation of the heart tube. (A) The embryo starts as a flat disc containing the three germ layers, the ectoderm (Ecto), mesoderm (Meso), and endoderm (Endo). (A–A‴) With ongoing folding of the embryo, the embryonic gut that runs from the stomatopharyngeal membrane (SM) to the cloacal membrane (CM) is formed. The heart (HT) becomes positioned ventrally to the foregut (FG), caudally to the head, and cranially to the umbilical cord and transverse septum (TS). HN, Hensen's node or primitive node. (B) Division of the heart-forming field into the first heart field (1), which will give rise to the linear heart tube and the second heart field (2), which will remain in continuity with the first heart field during subsequent development and from which cardiomyocytes are added to the developing heart. In reality, the strict borders drawn here are gradual. PM, pharyngeal mesoderm. (C–G) Formation of the heart tube from a flat horseshoe-shaped cardiac crescent to a tube. Folding of the embryo brings the lateral portions of the cardiac crescent (red line) together to form the ventral part of the heart tube, while the medial portions of the cardiac crescent (blue line) will form the dorsal part of the heart tube, which is suspended from the foregut by the dorsal mesocardium (DM). After the DM closes and the suspension from the foregut is lost, cells of the second heart field can only be added to the heart via the arterial and venous poles (AP and VP, respectively). (Source: Source: Sylva et al. [24]. Reproduced with permission of Wiley.)

lies between the myocardium and endocardium. The initial heart tube is therefore a tubular structure with an inner endocardial layer, a middle layer of cardiac jelly, and an outer myocardial layer.

Flow in the heart tube is unidirectional. Cardiac contractions start around day 22, and circulation through the embryo begins around day 26. Because the highest automaticity is found at the venous pole, a slow peristaltic contraction moves the blood from the venous to the arterial pole.

Abnormalities of heart tube formation

Clearly, failure of the heart tube to develop (*acardia*) leads to fetal demise, and as shown in the zebrafish, failure of the bilateral heart fields to fuse results in *cardia bifida* (two separate hearts in lateral positions) [27].

KEY POINTS: FORMATION OF THE HEART TUBE

- The primitive heart tube forms during the fourth week of development.
- Contractile activity initiates around day 22 and circulation through the embryo begins around day 26 of development.
- Failure of the heart tube to develop results in fetal demise.

Cardiac looping

Looping is a crucial process in cardiac morphogenesis that brings the tubular configuration of the primitive circulation into the correct conformation for chamber specification, septation, and the creation of systemic and pulmonary pathways [26,28]. The heart is not only the first organ to function, but is also the first to develop a bilateral asymmetric form. Cardiac asymmetry is attained during the process of looping.

At first, the heart tube is straight in the ventral midline with paired venous limbs at its caudal end and a single arterial outlet connected to the aortic sac and pharyngeal arch arteries at its cranial end (Figure 4.4) [29,30]. Looping begins with ventral bending (from dorsal to ventral) and the loss of the dorsal mesocardium, which suspends the heart tube from the foregut (ventral pharynx); these changes transform the straight tube into a curved tube (Figure 4.5). This is followed by rotation around the craniocaudal axis to the right (*dextro-* or *D-looping*), bringing the left side of the tube to a ventral (front) position, which is seen as a C-shaped loop with the convexity to the right in a ventral, two-dimensional view [26]. At this stage, the junction of the inflow and outflow limbs is at the deepest convexity. Externally, the junction corresponds to the bulboventricular groove, and internally it corresponds to the bulboventricular fold [31]. Subsequent looping produces a ventral, two-dimensional, S-shaped loop (Figure 4.6). The heart tube lengthens as cells are added in a continuous stream to the venous (inflow) and arterial (outflow) poles by the addition of myocardium (cardiomyocytes) and endocardium from the SHF in the adjacent pharyngeal mesoderm. The poles are the only entryway for new cells from the SHF [32]. The ventricular bend then shifts caudally from its cranial position above the atria, and the inflow region shifts cranially, thereby resulting in convergence of the inflow and outflow poles. After looping, there is rotation (untwisting) of the outflow tract, which results in a leftward shift of the outflow tract. The complex process of cardiac looping is summarized in schematic form in Figure 4.7. *Wedging* is the process in which the aorta will come to nestle between the mitral and tricuspid valves and behind the pulmonary trunk (Figure 4.8) [28]. When looping is complete, the named segments of the heart (which are extremely variable between authors) are the sinus venosus, common atrium, atrioventricular (AV) canal, presumptive left ventricle, presumptive right ventricle, conus arteriosus, and truncus arteriosus (frequently referred to as the conotruncus) [33].

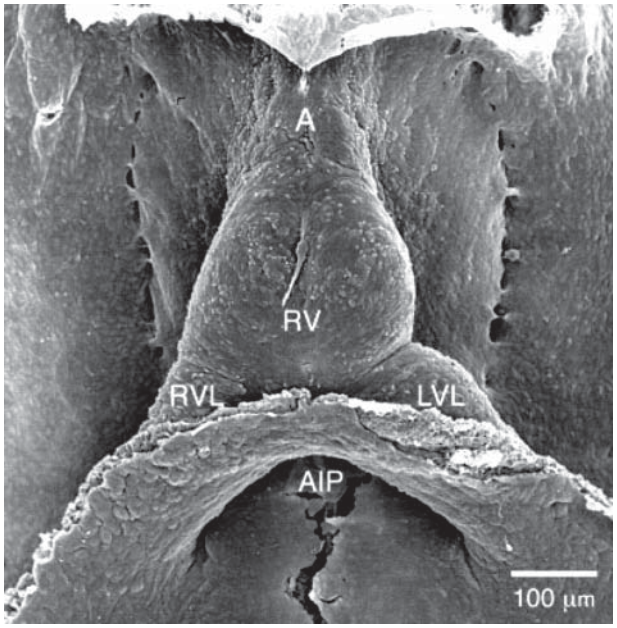


Figure 4.4 Straight heart tube. Scanning electron micrograph of a chick embryo (HH-stage 9), viewed from the front, showing the "straight heart tube" with paired venous limbs at its caudal end and an arterial outlet at its cranial end, which is connected to the aortic sac. A, arterial outlet; AIP, anterior intestinal portal; LVL, left venous limb; RV, primordium of the trabeculated portion of the morphologic right ventricle; RVL, right venous limb. (Source: Source: Männer [26]. Reproduced with permission of Wiley.)

Abnormalities of cardiac looping

Cardiac looping is associated with breaking of the initial bilateral symmetry of the embryo and establishment of the left–right axis [28,30]. The left–right axis is established during gastrulation by nodal cilia at the anterior border of the primitive streak. The cilia sweep from right to left, resulting in leftward flow of extracellular fluid which concentrates a putative secreted factor on the left side of the embryo. Binding of this factor to its receptors triggers asymmetrical gene at the node [28] and expression of *Nodal* (a member of the TGFβ family [34]. *Pitx2c* (a member of the homeobox gene transcription factor family) is a key regulator of cardiac left–right patterning that acts downstream of *Nodal*.

Left–right signaling pathways determine not only the direction of looping and the topology of the future ventricular chambers but also the proper development of the atria, the arterial and venous poles, and the systemic vasculature. Abnormalities in left–right patterning increase the incidence of cardiac malformations in both D- and L-loop hearts; typical examples include mirror imagery, atrial isomerism, discordant connections, and heterotaxy [35]. The left–right signaling cascade is hierarchical in that

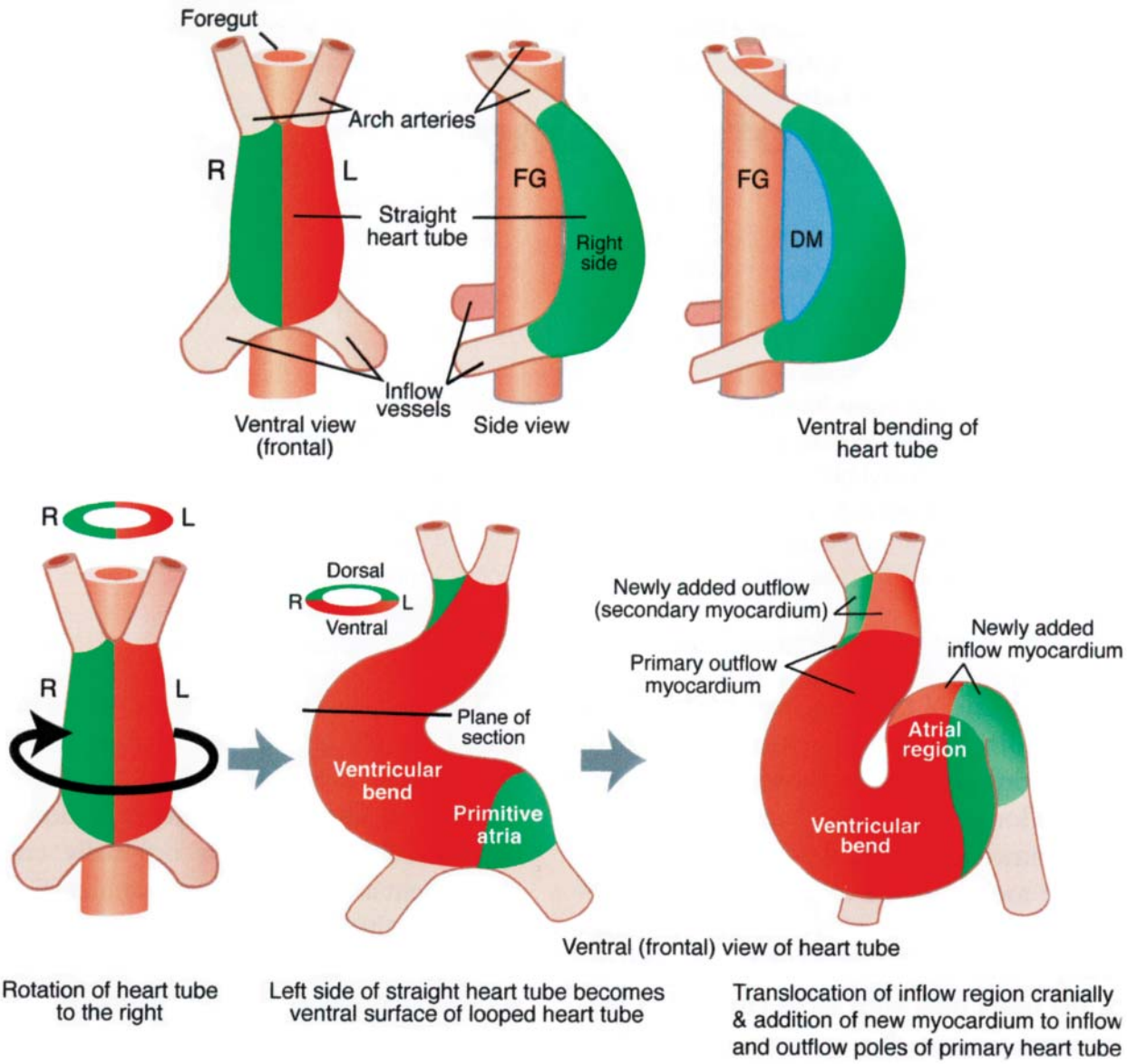


Figure 4.5 Steps in looping of the heart tube. The heart tube forms ventral to the foregut and is open to it at first. Then the heart tube is suspended at its nascent inner curvature from the ventral foregut by the dorsal mesocardium which quickly disappears. Ventral bending occurs first, followed by rotation to the right which brings the left side of the tube to the front and the inner curvature to the left side. Subsequent looping to form the S-shaped loop involves addition of cells at the inflow and outflow poles. DM, dorsal mesocardium; FG, foregut. (Source: Kirby [11]. Reproduced with permission of Oxford University Press.)

abnormalities high in the cascade result in randomization of situs, whereas abnormalities lower down, which are associated with tissue-specific signaling, produce discordant connections [24].

Normal cardiac looping to the right, referred to as *dextro-looping* or *D-looping*, positions the right ventricle towards the right side and leaves the heart lying predominantly in the left hemithorax with a leftward apex (*levocardia*) (Figure 4.9, left panel). *Situs solitus* refers to normal looping with the liver, stomach, and spleen in their normal positions. Rotation around the craniocaudal axis to the left results in a *levo-loop* (*L-loop*) heart (Figure 4.9, right panel), in which the right ventricle is positioned towards the left side of the body and the left ventricle towards the right side. *Congenitally corrected transposition of the great arteries* (CCTGA) arises when the heart (ventricle) loops to the left but the atria and outflow receive correct left–right signals, resulting in both AV and ventriculoarterial (VA) discordance. *Situs inversus* refers to an L-loop heart with mirror-image reversal, which means the heart lies predominantly in the right hemithorax with a rightward apex (*dextrocardia*) and there is mirror-image reversal of the liver, stomach, and spleen. *Mesocardia* refers to a midline heart with the

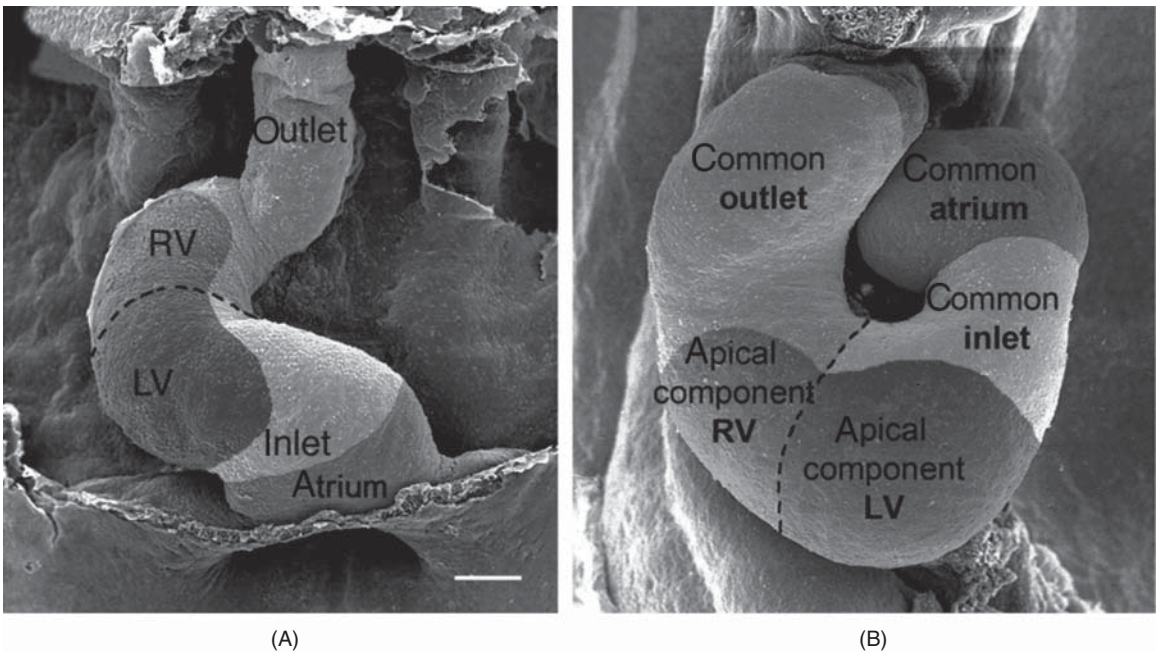


Figure 4.6 Looping morphogenesis. Scanning electron micrographs of embryonic chick hearts, viewed from the front, showing the main positional changes of the developing heart chambers of higher vertebrate embryos during cardiac looping. (A) "C"-shaped loop at early stages (HH-stage 12). (B) "S"-shaped loop at advanced stages (HH-stage 17/18) of cardiac looping. RV, right ventricle; LV, left ventricle. (Source: Männer [30]. Reproduced with permission of Elsevier.)

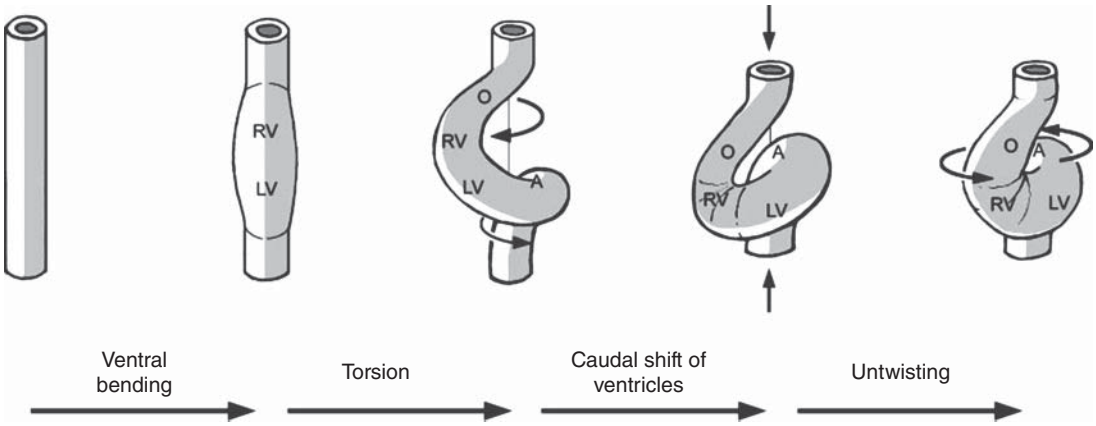


Figure 4.7 Ventricular looping. Schematic drawing (frontal views) of the four components of normal ventricular looping: (1) ventral bending transforms a straight tube into a curved tube whose outer curvature is formed by its ventral wall; (2) torsion around its original cranio-caudal axis transforms a curved tube into a helically wound loop which appears C-shaped in frontal views; (3) caudal shift of the ventricular segment; (4) untwisting is characterized by ventral and leftward shift of the proximal outflow tract, ventral shift of the primitive right ventricle, and rightward shift of the atrioventricular canal. A, common atrium; LV, embryonic left ventricle; O, outflow tract; RV, embryonic right ventricle. (Source: Männer [26]. Reproduced with permission of Elsevier.)

apex pointing inferiorly or anteriorly. Mesocardia and dextrocardia can be associated with a normal or abnormal arrangement of cardiac structures. *Atrial isomerism* refers to a bilaterally symmetrical pattern of the atrial appendages (i.e., bilateral leftness or rightness) and is usually associated with severe complex cardiac malformations [28]. *Mixed situs* occurs when some organs, or components thereof, have normal situs and others have situs inversus. This usually results in complex heart defects known as *heterotaxia* or *heterotaxy* syndromes (discussed later in the chapter).

KEY POINTS: CARDIAC LOOPING

- Cardiac looping represents a crucial process in cardiac morphogenesis that determines the shape of the heart.
- The process of cardiac looping is complex, resulting in right–left asymmetry in the embryo.
- Normal cardiac looping is to the right, referred to as dextro- or D-looping; abnormal looping to the left results in levo- or L-looping.

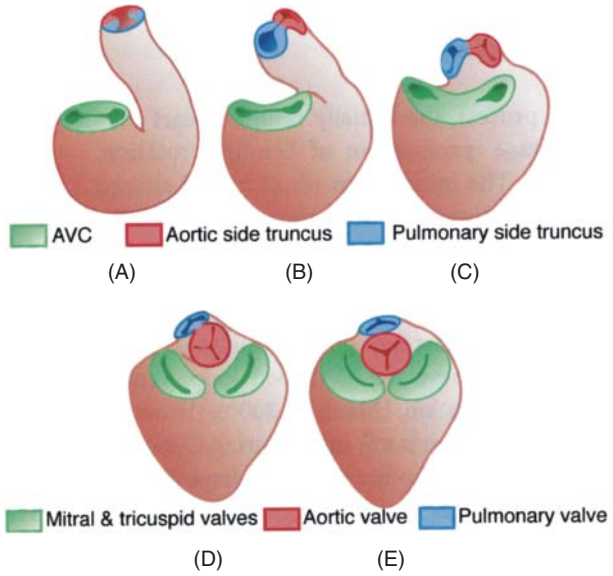


Figure 4.8 Steps in aortic wedging (A–E). The aortic side of the outflow tract nestles between the mitral and tricuspid valves as the outflow myocardium is remodeled. AVC, atrioventricular canal. (Source: Kirby [11]. Reproduced with permission of Oxford University Press.)

Cardiac septation

Cardiac septation begins after looping of the heart tube. It consists of four contemporaneous processes that occur between 27 and 37 days of development, dividing the heart into four chambers and creating separate systemic and pulmonary circulations [36]. Septation is attributable to the muscular septa in the atrial and ventricular chambers, the AV endocardial cushions, the outflow tract endocardial cushions, and the dorsal mesenchymal protrusion.

Atrial septation

Atrial septation takes place in phases to maintain right-to-left atrial shunting and involves the septum primum, septum secundum, and AV canal (AVC) septum. The *primary atrial septum* (septum primum) grows as a muscular crescent from the craniodorsal wall of the atrium on the right of the pulmonary pit towards the AV endocardial cushions (Figure 4.10). The leading edge of the septum primum is covered by a mesenchymal cap produced by the epithelial-to-mesenchymal transformation of the endocardium covering the septum [32]. This mesenchymal cap is continuous with the protrusion of the dorsal mesocardium (dorsal mesenchymal protrusion), the dorsal (superior) AV endocardial cushion, and the ventral (inferior) AV endocardial cushion [24]. The communication between the leading edge of the septum primum and the AV cushions is known as the *primary atrial foramen* (ostium primum), which closes when the septum primum becomes contiguous with the fused superior and inferior AV endocardial cushions. Communication between the left and right atria is maintained by the detachment of the septum primum from the roof of the atrial cavity to produce a secondary atrial foramen (ostium secundum) [37]. The *secondary atrial septum* (septum secundum) is formed by folding of the dorsal wall between the primary atrial septum and the left leaflet of the sinoatrial valve. The septum secundum does not fuse with the AV cushions but remains open as the *foramen ovale*. The cranial portion of the septum primum remains as a flap valve, which fuses with the edges of the foramen ovale after birth to form the fossa ovalis [32]. The muscular septum between the inferior rim of the fossa ovalis and the AV valves is called the AVC septum.

Early in development, the *venous pole* of the heart has two channels (the left and right horns of the sinus venosus), returning blood from the embryo (via the cardinal, vitelline, and umbilical veins) to the sinus venosus and common atrium. During the convergence phase of looping, the common atrium expands to the right and left, forming two lateral pouches that will become the right and left atrial appendages [26,38]. Remodeling results in the sinoatrial junction shifting to the right side of the common atrium. The sinus venosus, including its right horn, and the sinoatrial junction become incorporated into the dorsal (back) wall of the right atrium (Figure 4.11). The sinoatrial junction has left and right craniocaudally oriented valves (venous valves) that meet cranially to form the septum spurium [38]. As the distal portion of the left superior vena cava regresses, the left horn of the sinus venosus becomes smaller and is incorporated into the developing AV groove to become the coronary sinus. The dorsal (back) wall of the left atrium is also formed by incorporation of the pulmonary vein and its surrounding myocardium [32,38].

Defects in atrial septation

The most common cause of an atrial-level shunt is *a secundum atrial septal defect* (ASD), which is located within the region of the fossa ovalis. It is usually due to a deficiency of the septum primum but, in rare cases, can be caused by a deficiency of the septum secundum [39].

Failure of the septum primum and septum secundum to fuse completely during infancy results in a *patent foramen ovale* (PFO). As long as the left atrial pressure exceeds the right atrial pressure and the flap valve is large enough to cover the boundaries of the fossa ovalis, the foramen remains functionally closed (probe patent foramen).

An *ostium primum defect* results from failure of the septum primum to fuse with the endocardial cushions. The defect is outside the confines of the fossa ovalis and extends from the inferior limbus of the fossa ovalis to the crest of the interventricular septum. An ostium primum defect is part of the family of AVC defects, also referred to as AV septal and endocardial cushion defects, and may occur in isolation or in association with other abnormalities of the AV junction.

A *sinus venosus defect* occurs in the area derived from the embryologic sinus venosus (posterior aspect of the right atrium) and is an interatrial communication in which the right atrium connects to the left atrium through one or

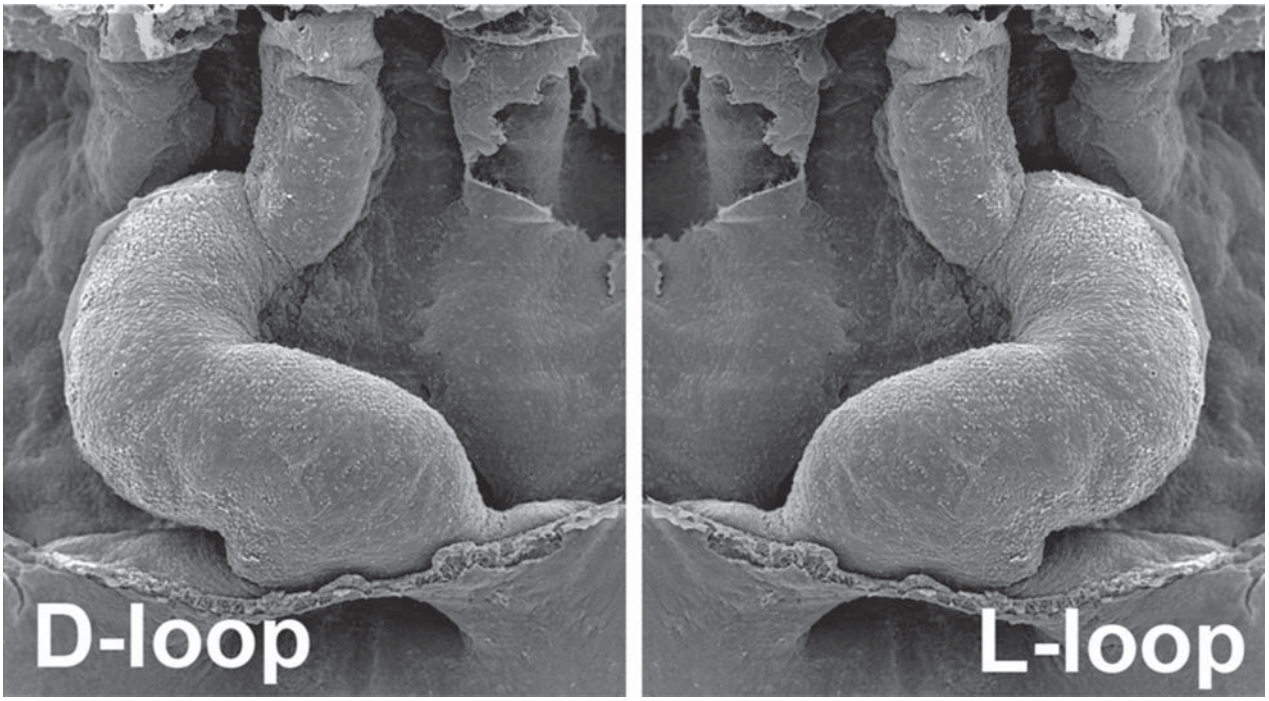


Figure 4.9 Handedness of the cardiac loop. Scanning electron micrographs of embryonic chick hearts, viewed from the front, showing the so-called D-loop (dextral-loop) and L-loop (levo-loop) configurations ("C-shaped" loops; HH-stage 12).

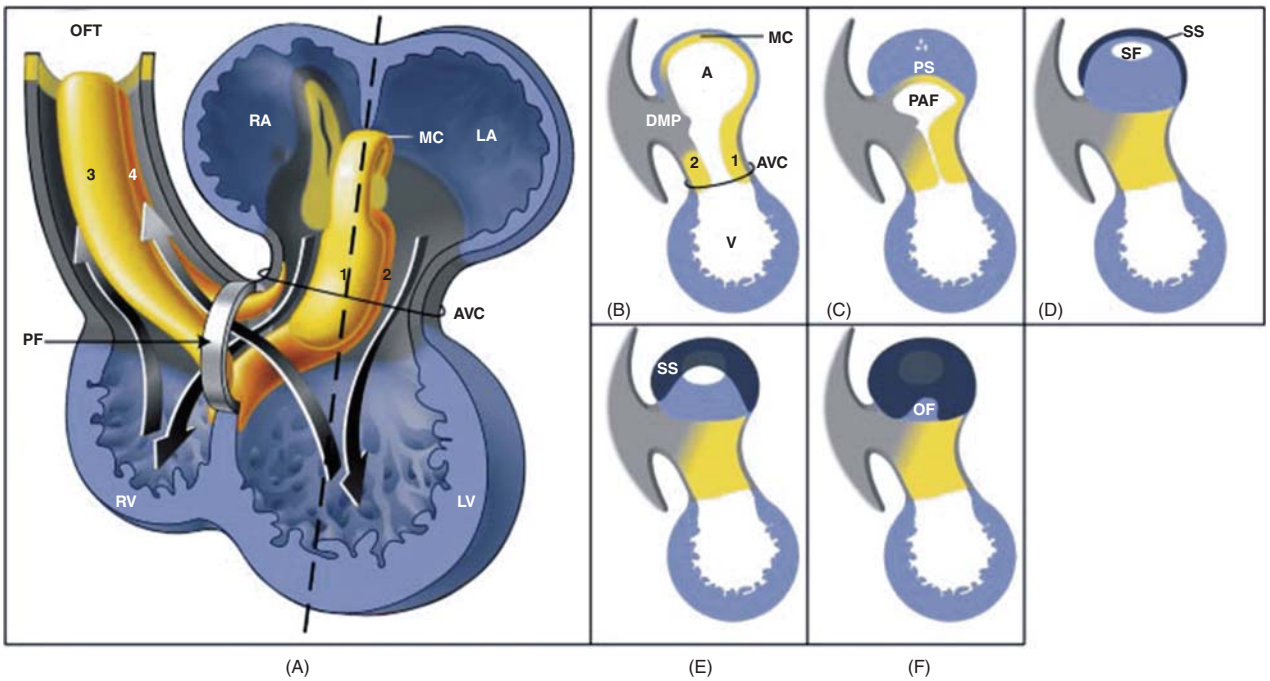


Figure 4.10 Schematic drawing illustrating septation of the atria and primary foramen. (A) Chamber-forming heart with the atrioventricular canal (AVC) and outflow tract (OFT) cushions and ridges. The two arrows going down through the AVC into the ventricle represent blood flow during diastole. The two arrows pointing toward the OFT represent blood flow during systole. Note that the primary foramen (PF) is the crossroad of the blood running from the right atrium (RA) to the right ventricle (RV), and the blood running from the left ventricle (LV) to the OFT. (B–F) Sagittal sections at the level of the dotted line in (A). (B) The ventral and dorsal endocardial cushions (1 and 2, respectively) are growing toward each other. (C) The primary atrial foramen (PAF, ostium primum) is closing due to ingrowing of the primary atrial septum (PS, septum primum), with its mesenchymal cap (MC), the dorsal mesenchymal protrusion (DMP), and the endocardial cushions. (C,D) In the PS, small holes appear and merge to form the secondary foramen (SF, ostium secundum). (D–F) The secondary septum (SS, septum secundum) grows to the right side of the PS covering the SF and the rest of the PS, and leaving at the right surface of the atrial septum only the oval fossa (OF) uncovered. A, atrium; LA, left atrium; V, ventricle; 3 and 4, septal and parietal outflow tract ridges, respectively. (Source: Sylva et al. [24]. Reproduced with permission of Wiley.)

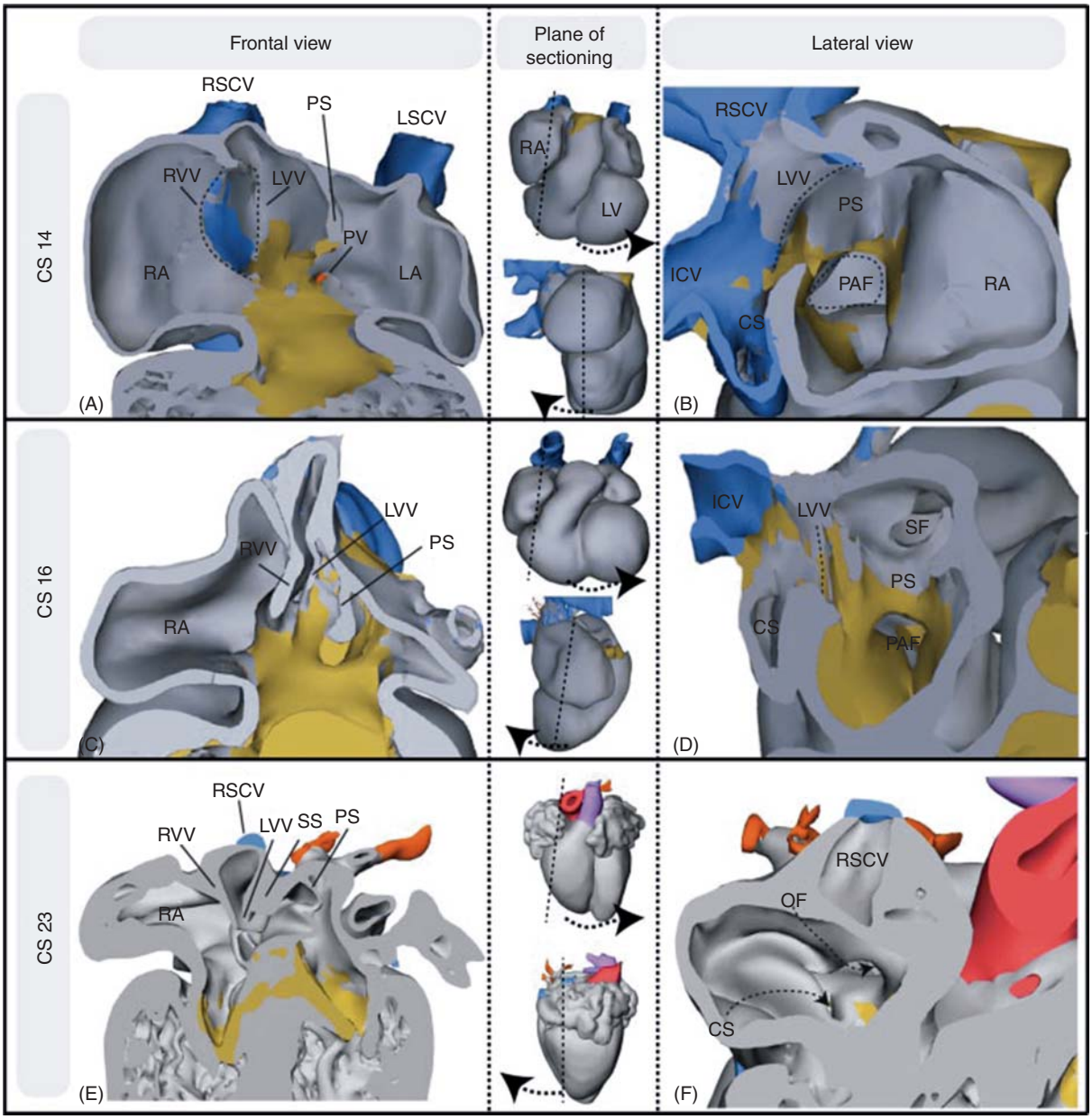


Figure 4.11 Formation of the venous pole. (A–F) Cross-sections of three-dimensional (3D) reconstructions of human hearts (gray, myocardium; blue, systemic veins; orange, pulmonary veins; yellow, cardiac mesenchyme). (A, B) Developing right and left atrium (RA, LA); the RA is connected to both the right superior (RSCV) and inferior caval vein (ICV) as well as the left superior caval vein (LSCV), via the coronary sinus (CS). At this stage the entire systemic venous pole is connected to the right atrium through one orifice, flanked by the left and right venous valves (LVV and RVV). The primary septum (PS) is growing to the right of the opening of the pulmonary vein (PV). (C,D) The RSCV and CS are still connected to the atrium via a single orifice, which has now been muscularized. The secondary foramen (SF) appears in the primary septum. (E,F) All veins connect separately to the atrium via myocardialized orifices. The primary atrial foramen (PAF) is closed and the secondary septum (SS) is growing between the PS and the LVV, which is already partially fused to the secondary septum. The RVV can now be separated in a part that flanks the CS and a part that flanks the RSCV, the future Thebesian and Eustachian valves, respectively. OF, oval foramen; CS, Carnegie stage (noted on left margin of figures). (Source: Sylva et al. [24]. Reproduced with permission of Wiley.)

more of the pulmonary veins. The most common location for this defect is between the right upper pulmonary vein and the cardiac end of the superior vena cava (SVC type), although in rare cases the right lower/and or middle pulmonary veins and more caudal atrial wall are involved (inferior vena cava [IVC] type) [39].

A *coronary sinus defect* occurs when the tissue between the coronary sinus and the left atrium is either partially or completely absent (unroofed), resulting in communication between the right and left atria via the coronary sinus orifice. The left-to-right shunt causes enlargement of the coronary sinus orifice.

A *common atrium* is caused by the absence of the septum primum, septum secundum, and atrial portion of the AVC septum and is usually associated with heterotaxy syndrome [39].

Ventricular septation

After looping of the heart tube occurs, differentiation and re-initiation of cell division by the primary myocardium of the outer curvature causes the ventricles to expand caudally in a pouch-like fashion on either side of the bulboventricular groove (Figure 4.12). De Boer and colleagues [40] have shown that growth of the trabeculae occurs by cellular proliferation at the bases, causing the ventricles to expand or "balloon outwards" (ballooning model of chamber formation). Disappearance of the cardiac jelly results in the formation of trabeculations on the luminal side, producing a spongy-type myocardium. Compact myocardium forms later when epicardially derived fibroblasts infiltrate the epicardial side, at which time proliferation in the trabeculations ceases.

The *muscular* portion of the interventricular septum is formed by apposition and merging of the medial walls of the expanding ventricles, with cells added mainly from the adjacent left ventricular free wall [24,36]. It is initially crescent-shaped, extending from the inferior (ventral) AVC cushion posteriorly to the superior (dorsal) AVC cushion anteriorly. The space between the free rim of the muscular septum and the fused AV cushions is the *primary interventricular foramen*. Although the primary interventricular foramen allows for communication between the primitive left and right ventricles, initially, blood from the primitive atrium can only reach the primitive right ventricle via the interventricular foramen. It is only after the AV junction develops that the right atrium will communicate directly with the right ventricle. Closure of the interventricular foramen occurs by fusion of three structures: the superior and inferior endocardial cushions, the muscular interventricular septum, and the endocardial cushions of the outflow tract (conal cushions). The site where these three structures fuse constitutes the *membranous* part of the ventricular septum. Ventricular septation is usually completed between days 38 and 45 of gestation [41].

Defects in ventricular septation

Ventricular septal defects (VSDs) may be found in isolation or may co-exist with other congenital cardiovascular anomalies. Because the ventricular septum is composed of three components (muscular, AVC endocardial cushion, and outflow tract [conal] cushion), defects at the ventricular level may result from a deficiency of one or more of these structures and/or from their malalignment.

The most common VSDs are those that occur in the *muscular* portion of the interventricular septum. This type of VSD is surrounded by a rim made completely of muscle. They are often multiple and may be located anywhere in the muscular septum (apical, anterior, mid, or posterior).

The *membranous septum* is a small, translucent structure. It is adjacent to the anteroseptal commissure of the tricuspid valve when viewed from the right side, and it is below the non-coronary leaflet of the aortic valve when viewed from the left. Small defects may spontaneously close after birth due to the presence of the surrounding fibrous tissue (also referred to as aneurysmal tissue). Defects that extend beyond the boundaries of the membranous septum are called *para-* or *perimembranous* defects. Membranous VSDs are closely associated with the bundle of His, increasing the risk of causing conduction disturbances during repair.

A *conoventricular* or *subaortic* defect is situated between the conal and muscular portions of the ventricular septum and is also close to the bundle of His [41]. These defects are often related to malalignment of the muscular and conal portions of the ventricular septum.

A *subpulmonary*, *conal*, *supracristal*, or *doubly committed subarterial* defect is located in the outflow tract (conal septum) just below the pulmonary valve. Fibrous continuity between the aortic and pulmonary valves is frequently present. The aortic valve (right cusp or non-coronary cusp) may prolapse into the defect, which may result in aortic regurgitation.

A defect that opens to the *inlet* portion of the right ventricle may be perimembranous, muscular, or AV [42]. The origin of the AV node and the course of the AV bundle (His) differ for these types, increasing the risk of injury during surgical repair.

A *common* or *single ventricle*, defined as the presence of two AV valves with one ventricular chamber or a large dominant ventricle with a diminutive or hypoplastic opposing ventricle may result from various different mechanisms. The pathology may be due to the arrest of or a defect in interventricular septation or from poor alignment of the common AV valve with the ventricles [43]. A wide spectrum of functional single ventricles is recognized. These include double-inlet single ventricle (usually left), defects resulting from atresia or absence of either the right or left AV valve, such as tricuspid atresia, mitral atresia (part of hypoplastic left heart syndrome [HLHS]), those with an atretic semilunar valve (HLHS, pulmonary atresia with intact ventricular septum), unbalanced common AVC defects, and some forms of double-outlet right ventricle.

AV canal septation and AV valve development

The cardiac jelly at the AV junction (and proximal outflow tract) forms into mounds by the myocardial synthesis of extracellular matrix. The endocardial cushions arise from the cells of the endocardium overlying these swellings that invade the cardiac jelly and undergo endocardial-to-mesenchymal transformation into fibroblast-like mesenchymal cells [44]. Prior to valve formation, the endocardial cushions and underlying myocardium prevent the backflow of blood. An inferior endocardial cushion is associated with the outer curvature of the looped heart, and a superior cushion is associated with the inner curvature (Figure 4.10) [29]. Central fusion of the inferior and superior cushions forms the AV septum,

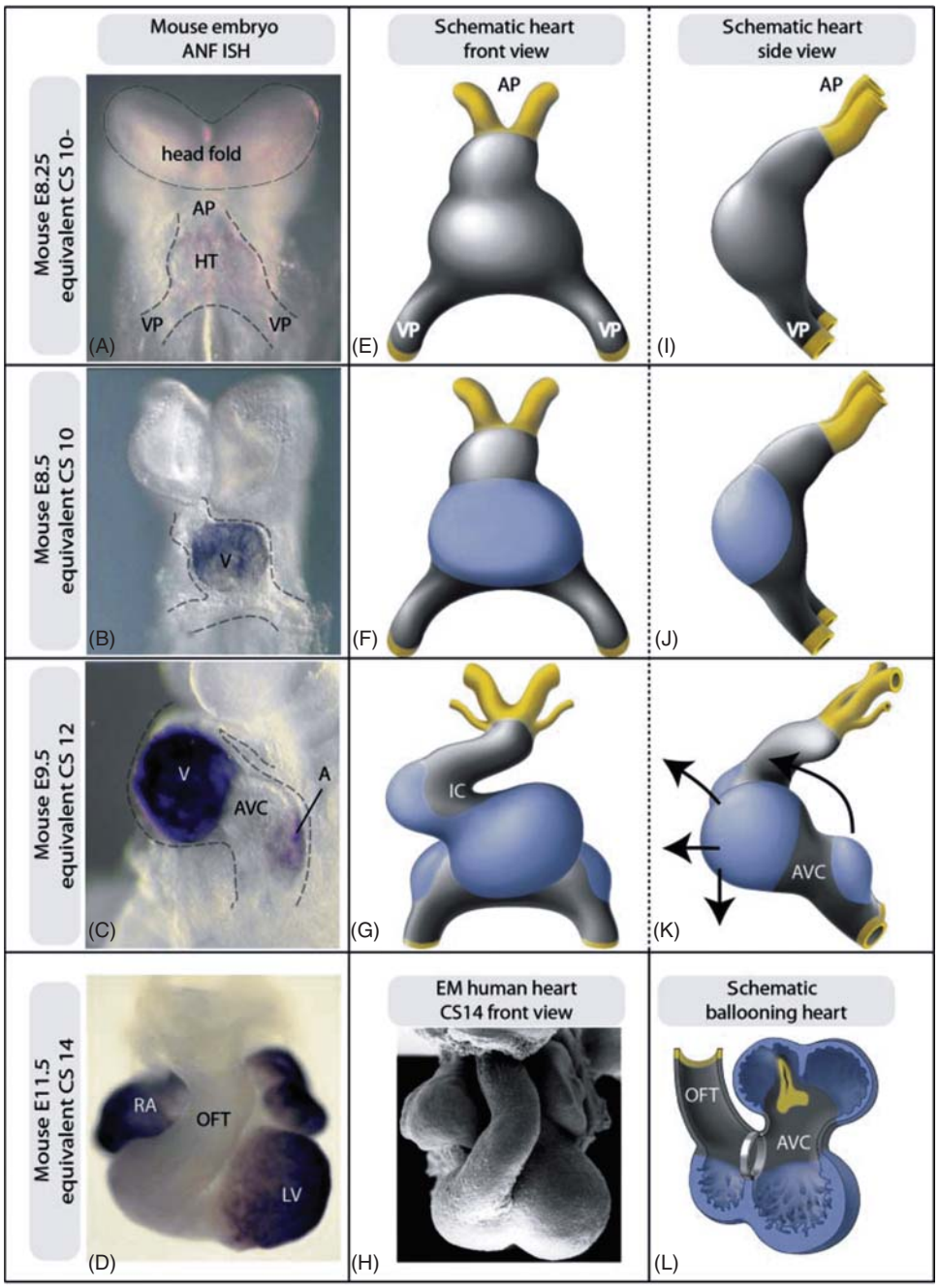


Figure 4.12 Formation of the cardiac chambers. (A–D) Developmental series of mouse embryos. Whole-mount RNA *in situ* hybridization for the embryonic chamber marker atrial natriuretic factor (ANF) is used as a marker for differentiation into chamber myocardium. (E–G) and (I–L) Schematic drawings of these chamber-forming hearts. Gray, primary myocardium; blue, chamber-forming myocardium; arrows in K indicate the expansion of the chambers eventually leading to the adult configuration, with the ventricles positioned ventro-caudally to the atria. (H) Electron micrograph of a CS14 human heart, demonstrating the similarity with the mouse E11.5 heart and the schematic shown in (L). For didactic purposes, in the schematic in (L), the outflow tract is hinged toward the right side, *in vivo* it is positioned ventrally to the heart, as depicted in (D) and (H). (A, E, I) The heart tube (HT) consists solely of primary myocardium from the venous (VP) to the arterial pole (AP). (B, F, J) The first chamber to start ballooning is the embryonic ventricle (V) at the outer curvature of the heart. (C, G, K) The heart tube has started to loop and acquire an S shape. An embryonic left and right ventricle are now visible. The atria (A) also start to balloon towards the left and right side. The myocardium of the outflow tract (OFT), inner curvature (IC), and atrioventricular canal (AVC) remains as the primary myocardium. RA, right atrium; LV, left ventricle; CS, equivalent Carnegie stage noted in the left margin of figures. (Source: Sylva et al. [24]. Reproduced with permission of Wiley.)

thereby separating the AVC into the left (mitral) and right (tricuspid) orifices [11]. The *atrial portion of the AV septum* extends from the level of the valve annuli to fuse with the primary atrial septum, whereas the *ventricular portion of the AV septum* extends from the level of the valve annuli to form the inlet portion of the interventricular septum. The AVC expands to the right, as does the right ventricle, to allow for direct communication between the presumptive right atrium and the presumptive right ventricle. Smaller cushions develop on the lateral walls (left and right) of the AVC.

The septal leaflet of the tricuspid valve and the anterior leaflet of the mitral valve are derived from the fused inferior and superior endocardial cushions, whereas the mural leaflets are derived from the lateral cushions [45]. Mature AV valves and the subvalvular apparatus are formed by cavitation and remodeling of the cushions and excavation of the underlying ventricular myocardium to form leaflets and chordae tendinae (Figure 4.13) [45,46]. Late in development, the primitive leaflets undergo lengthening and delamination with the disappearance of the myocardial layer.

After the endocardial cushions have fused, the fibroblast-like cells of the cushions are replaced by myocardial cells in a process called myocardialization. Fusion of the nonmyocardial mesenchymal cushions and myocardialization create part of the atrial septum, ventricular septum, and conal septum, as well as the substrate for the crux of the heart [47].

Defects of the AVC

The endocardial cushions of the AVC contribute to the formation of the atrial septum, the ventricular septum, and the mitral and tricuspid valves. The structures derived from the endocardial cushions can have varying degrees of abnormalities, producing a spectrum of lesions called endocardial cushion defects (as previously noted, they are also referred to as AVC or AV septal defects).

At the mildest end of the spectrum is an isolated *cleft in the anterior leaflet of the mitral valve*. An *ostium primum ASD* is the result of improper fusion of the superior endocardial cushion with the septum primum; although there are two distinct annuli, there is frequently a mitral valve cleft. An *inlet* or *AVC-type VSD* occurs when the inferior endocardial cushion does not fuse with the muscular component of the ventricular septum. A *transitional AVC defect* is typically an ostium primum defect with a very small to moderate (restrictive) inlet VSD, which is often occluded by AV valve tissue. A *complete AVC* (CAVC) *defect* comprises an ostium primum ASD, an inlet VSD, and a common AV valve (i.e., the valve leaflets are shared between the left and right ventricles, otherwise referred to as bridging leaflets) in which the leaflets are not adherent to the crest of the ventricular septum. With a CAVC defect, there is reduced wedging of the aortic valve and displacement of the common hinge plane of the AV valve towards the apex so that the apex-to-outlet ventricular dimension is increased and the inlet-to-apex distance is decreased, resulting in a "gooseneck" deformity of the left ventricular outflow tract [48]. In an *unbalanced CAVC defect*, usually one ventricle is hypoplastic and the other receives most of the AV valve tissue because of *straddling* (insertion of chordae in the opposite ventricle) or *override* (insertion of chordae to the crest of the septum or the appropriate ventricle). AVC defects may be isolated or may appear as one element of a more complex lesion or syndrome. Approximately 40% of patients with trisomy 21 (Down syndrome) have AVC defects [46].

Ebstein anomaly is the most important cause of congenital tricuspid regurgitation and is thought to be due to abnormal delamination of the inlet zone of the right ventricle [49]. The septal and posterior leaflets do not attach to the annulus but are displaced downward toward the right ventricular apex. The portion of the right ventricle that extends from the true tricuspid annuls to the level where the septal and posterior leaflets attach is thin due to partial absence of myocardium and is termed the "atrialized" portion, whereas the trabecular and outlet portions make up the functional right ventricle. The anterior leaflet is large ("sail-like") and dysplastic and can obstruct the right ventricular outflow tract. Ebstein anomaly can be associated with abnormalities in left ventricular morphology, such as ventricular non-compaction and increased fibrosis of the wall and septum. Most patients with this anomaly have a PFO, and approximately 50% have an ASD [50]. Downward displacement of the leaflets is associated with discontinuity of the central fibrous body, thus producing a substrate for accessory AV connections and ventricular pre-excitation [49].

Tricuspid atresia is characterized by agenesis of the tricuspid valve and right ventricular hypoplasia. The region normally occupied by the tricuspid valve may be replaced by an atretic membrane, muscular tissue, or fibrofatty tissue, in which case an ASD would be necessary for survival. With normally related great arteries, blood passes to the lungs through a VSD into a small right ventricle and pulmonary artery, whereas with transposition of the great arteries, blood reaches the lungs directly from the left ventricle. Isolated *tricuspid stenosis* is exceedingly rare.

Mitral valve stenosis is most commonly associated with other left-sided obstructive lesions, HLHS being at the most severe end of the spectrum and coarctation of the aorta, aortic arch hypoplasia, and subvalvular or valvular aortic stenosis in Shone's complex occurring with varying severity. *Congenital mitral regurgitation* is more common than mitral stenosis and is usually associated with AVC defects.

Outflow tract septation and development of the semilunar valves

Cardiac neural crest cells are a subpopulation of the cranial neural crest and are crucial for normal cardiovascular development [22]. Cardiac neural crest cells contribute to the formation and remodeling of the aortic arch arteries, outflow tract septation, semilunar valvulogenesis, the

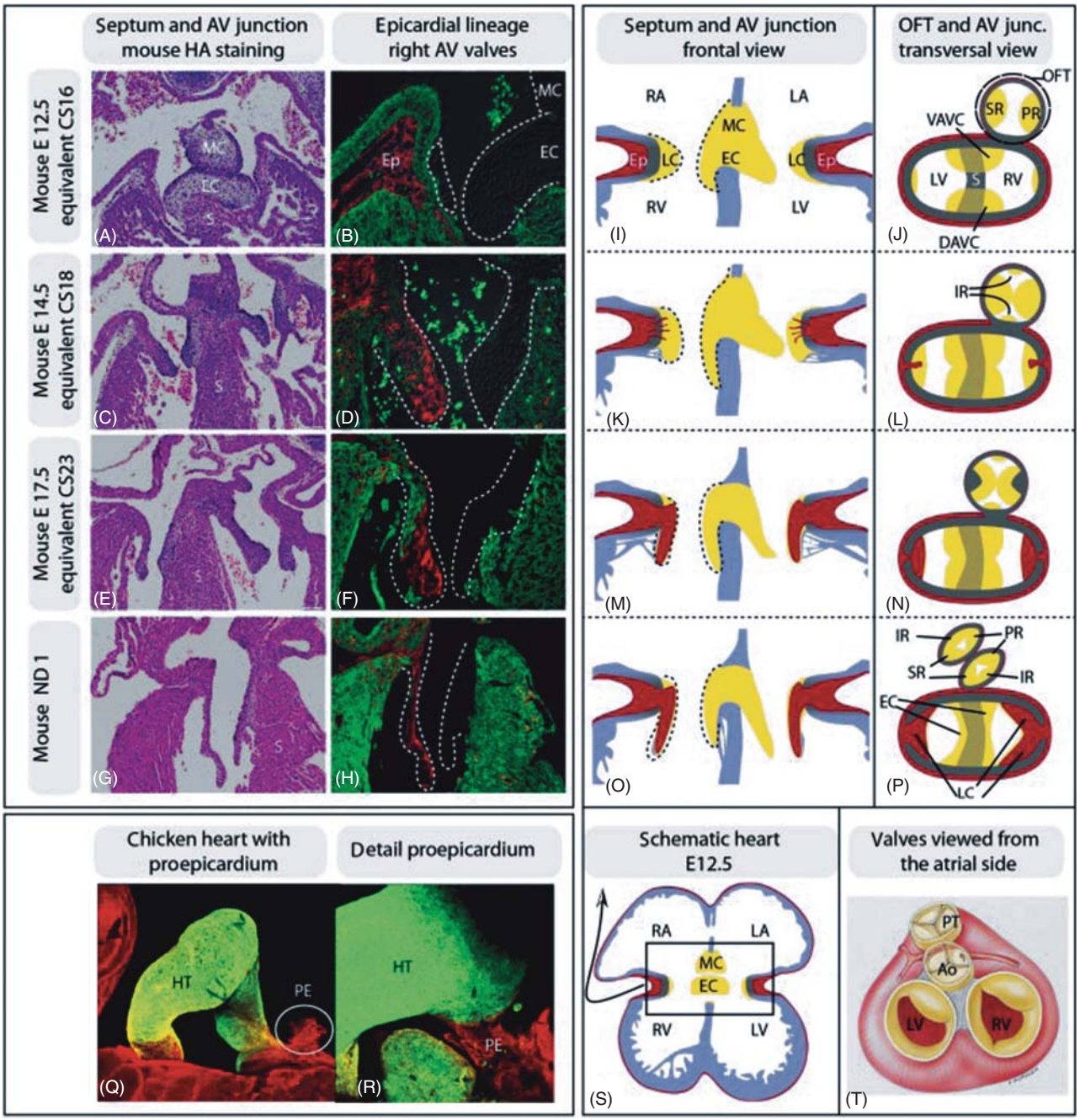


Figure 4.13 Development of the atrioventricular (AV) and outflow tract (OFT) valves and their contributing tissues. (A–H) Sections through mouse hearts in a plane comparable to the schematic heart in panel (S). (B, D, F, H) The lineage contributions of the epicardium is displayed at different developmental stages. The epicardial lineage marker WT1 was used; epicardial lineage is depicted in red, myocardium in green. (I–P) Schematic drawings of valve development in both the atrioventricular canal and outflow tract. Red, epicardium (Ep); gray, primary myocardium; and yellow, endocardial cushion tissue (EC). Note that in the outflow tract the cells are primarily neural crest-derived and not endocardial-derived as in the AV canal. (P) The contribution of the different cushions and ridges to the eventual valves (panel T) is depicted. (Q, R) Display the proepicardium (PE) in a 3-day-old chick embryo. (R) The PE is attached to the heart tube (HT) and spreading out to form the epicardium. Ao, aorta; DAVC, dorsal AV cushion; IR, intercalated ridge; LA, left atrium; LC, lateral cushion; LV, left ventricle; MC, mesenchymal cap; PR, parietal ridge; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; S, septum; SR, septal ridge; VAVC, ventral AV cushion. Equivalent Carnegie stage (CS) is noted in the left margin of figures. (Source: Sylva et al. [24]. Reproduced with permission of Wiley.)

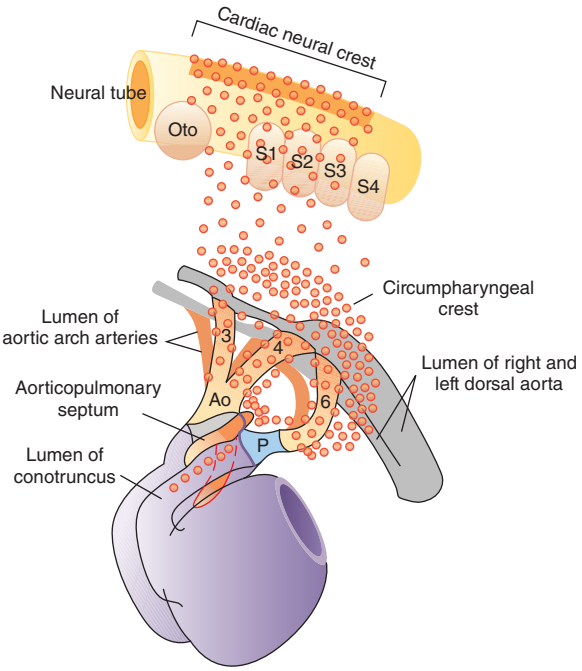


Figure 4.14 Cardiac neural crest. Migration of the cardiac neural crest to the circumpharyngeal ridge, caudal pharyngeal arches (3–6), and outflow tract depicted schematically. S1, S2, S3, S4, somites 1–4. (Source: Kirby [11]. Reproduced with permission of Oxford University Press.)

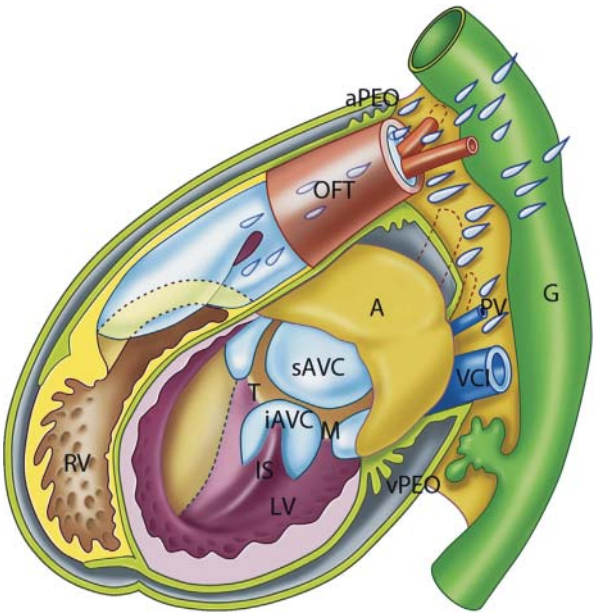


Figure 4.15 Schematic representation of the developing heart. Simplified model of a heart prior to ventricular septation. The roof of the atrium (A, light brown) is closed; therefore, atrial septation is not shown here. The anterior walls of the left ventricle (LV) and right ventricle (RV) are opened to reveal the inside. The interventricular foramen (primary foramen) is present. The inlet septum (IS) is connected to the inferior AV cushion (iAVC). The epicardium (olive green) covers most of the surface of the heart, but the venous proepicardial organ (vPEO; between liver and venous pole) and the arterial PEO (aPEO) surrounding the arterial pole are still present. The second heart field-derived part of the RV is shown in yellow, the endocardial cushions in light blue, neural crest cells in lavender, and the gut (G), including the liver, in green. AVC, atrioventricular canal; M, mitral ostium; OFT, outflow tract; PV, pulmonary vein; sAVC, superior AV cushion; T, tricuspid ostium; VCI, inferior cardinal vein. (Source: Gittenberger-de Groot et al. [55]. Reproduced with permission of Elsevier.)

development of cardiac neuronal tissue, and the insulation of the cardiac conduction system [51].

The outflow tract connects the primitive ventricle to the aortic arch arteries and is traditionally divided into three sections: the conus (proximal), the truncus (middle), and the aortic sac (distal) [52]. Septation of the outflow tract begins with the formation of a shelf of mesenchyme in the dorsal wall of the aortic sac in the area between the fourth and sixth pairs of aortic arch arteries [53]. This shelf, called the aorticopulmonary septum, elongates towards the truncus, thereby dividing the lumen of the aortic sac into the future intrapericardial portions of the aorta and pulmonary trunk. Cardiac neural crest cells migrate into pharyngeal arches 3, 4 and 6, and a subset of these cells migrates into the outflow tract (Figure 4.14). The outflow endocardial cushions are ridges of mesenchyme, formed by endocardial-to-mesenchymal transformation of the underlying endocardium, that spiral into the outflow tract. Mesenchymal cells from the pharynx, followed by neural crest cells, invade the truncal cushions to form two centrally placed columns, or prongs, in the shape of an upside-down "U" (Figure 4.15) [54]. These prongs will fuse with the aorticopulmonary septum distally and with the conal cushions proximally. Rotation of the developing pulmonary valve (see later) is associated with spiraling of the aorticopulmonary septum and prongs, so that the developing aorta will connect with the rightward and cranial component of the aortic sac and the developing pulmonary trunk will connect with the leftward and caudal component of the aortic sac [56].

The convergence of the inflow and outflow poles during looping combined with the rotation and wedging processes brings the atria and outflow vessels into concordance with the AV valves and ventricles [52,54]. In the conus, myocardial cells invade the cushions (myocardialization), which then bulge further into the lumen and subsequently meet and fuse in the midline. These conal cushions fuse most proximally with the AV cushion tissue and the crest of the muscular ventricular septum. Muscularization of the central conal cushion tissue and development of the adjacent aortic and pulmonary sinuses produces the *subpulmonary infundibulum* and a plane of space between the infundibulum and aortic root [56].

The developing pulmonary valve is initially posterior to and left of the developing aortic valve. Morphogenetic movement of the pulmonary valve (posterior to anterior, left of the aortic valve) brings it to its final position anterior and lateral to the aortic valve (Figure 4.8) [57]. This movement of the pulmonary valve is thought to be caused by the development of the subpulmonary conus (infundibulum), which also causes the pulmonary valve to be in a superior position relative to the aortic valve.

Early in development, both the subpulmonary conus and the subaortic conus are situated above the right ventricle. Following torsion and a leftward shift of the outflow tract, resorption and shortening of the subaortic conus causes the aortic valve to sink inferiorly and posteriorly so that it comes to lie directly over the left ventricle and in fibrous continuity with the mitral valve (Figure 4.8) [58]. The conversion from the primitive, single in-series circulation to the double in-series circulation takes place during the fifth week of development.

Following outflow tract septation, the semilunar valves are formed as the mesenchyme in the outflow cushions is remodeled into the trileaflet aortic and pulmonary valves. Initially, three pairs of ridges, consisting of mesenchymal tissue covered by endocardium, protrude into the lumen on each side of the divided truncus [54]. Valve sinuses are formed by excavation on the arterial (distal) face of the cusps. Thereafter, the leaflets are remodeled by mesenchymal apoptosis, blood flow, and shear stress to produce the delicate fibrous tissue seen in mature valves. Cells from the endocardium are the primary source of semilunar and AV valve fibroblasts, but fibroblasts derived from the epicardium also contribute to valve formation [53]. Although neural crest cells are found in the tips of the leaflets, their contribution to valve formation is not fully understood.

Abnormalities of outflow tract septation

The loss or dysfunction of cardiac neural crest cells produces a wide spectrum of conotruncal abnormalities that are associated with syndromes linking defects in the heart, face, and brain [52,54]. These include the 22q11 deletion syndromes, such as DiGeorge and velocardiofacial syndromes, CHARGE syndrome, fetal alcohol syndrome, retinoic acid embryopathy, Alagille syndrome, and Noonan and LEOPARD syndromes [52]. The association between thymus, thyroid, and parathyroid abnormalities in these syndromes is explained by the fact that the neural crest cells contribute to the connective tissue of these three organs. Additionally, abnormalities of the SHF also produce outflow tract defects [54].

Persistent truncus arteriosus results from a failure in outflow tract septation (conotruncus and aorticopulmonary septum) combined with a virtual absence of the subpulmonary infundibulum and, thus, a VSD [59,60] Typically, the aortic and pulmonary valves are fused to form a single semilunar truncal valve. The origin of the pulmonary arteries from the truncal root varies and is dependent on the degree of the septation deficiency. Incomplete outflow tract septation results in an *aortopulmonary window*. Aortoventricular tunnels are thought to result from abnormal excavation and maturation of the outflow cushions during the formation of the semilunar valves [56]. Unequal septation can result in either the aorta or pulmonary artery being *hypoplastic* relative to the other.

Tetralogy of Fallot is thought to result from underdevelopment of the subpulmonary infundibulum (conus) [61]. The smaller infundibulum causes anterior deviation of the conal septum and malalignment of the conal septum with the muscular ventricular septum, producing right ventricular outflow tract obstruction and a subaortic VSD [62]. The pulmonary valve is usually abnormal, and the reduced blood flow contributes, to some degree, to pulmonary artery hypoplasia. Some patients have *tetralogy of Fallot with pulmonary valve atresia* and varying degrees of hypoplasia of the main and branch pulmonary arteries.

Theories that have been proposed to explain *transposition of the great arteries* (TGA) include resorption of the subpulmonary conus, causing the pulmonary valve to move inferiorly and posteriorly so that it comes to lie above the left ventricle and in fibrous continuity with the mitral and tricuspid valves [57], and failure of the aorticopulmonary septum to spiral [63]. Dextro- or D-TGA refers to TGA with normal looping of the heart to the right, whereas L-TGA refers to looping of the heart to the left [64]. In D-TGA, there is AV concordance and VA discordance. *Congenitally or physiologically corrected TGA* is characterized by TGA and AV discordance (i.e., double discordance). In the more frequent form, referred to as L-transposition, there is levocardia with situs solitus of the atria and L-looping of the heart. The other form is a mirror image of the above with dextrocardia, inversion of the atria (situs inversus), and D-looping of the heart [65].

Persistence of both the subpulmonary and subaortic coni results in *double outlet right ventricle*, whereas a deficiency of both results in a *double outlet left ventricle* (very rare); in either case, there is almost always a VSD.

Fused or absent pulmonary commissures produce *pulmonary valve stenosis*, in which the valve is typically mobile and dome-shaped with a small and sometimes eccentric orifice [66]. *Critical pulmonary stenosis* is a severe form of pulmonary stenosis that is considered a ductal-dependent lesion because a patent ductus arteriosus (PDA) is essential for pulmonary blood flow.

Obstruction of the left ventricular outflow tract may occur at the valvular, subvalvular, or supravalvular levels. The most common aortic valve anomaly is a *bicuspid aortic valve* [2]. This malformation is also thought to be the most common cardiac defect (occurring in 1–2% of the population). It may be an incidental finding or may result in a clinical presentation in childhood or adult life, and it can occur in isolation or in association with left-sided obstructive lesions [67]. There are several variants, the most frequent being characterized by commissural fusion (most commonly between the coronary cusps), creating a functionally bicuspid structure, and the far less frequent "true" bicuspid valve. *Critical aortic valve stenosis* in the neonate is a ductal-dependent lesion, in that a PDA is necessary for systemic perfusion. The valve is usually unicommisural or bicommisural and incompletely differentiated with thickened, redundant, and rolled cusps and leaflets consisting of immature loose connective tissue (myxomatous) [68]. Dysplastic valves, rather than commissural fusion, obstruct the orifice. Severe aortic stenosis or *aortic atresia* can be part of a spectrum of left-sided obstructive lesions associated with hypoplasia of the left ventricle, ascending aorta and/or arch, mitral

valve stenosis or atresia, and endocardial fibroelastosis of the left ventricle (i.e., HLHS) [69].

Subvalvular aortic stenosis has a number of embryologic etiologies. Malalignment of the conal septum with the muscular interventricular septum results in posterior projection of the conal septum into the left ventricular outflow tract and an associated VSD. This pathology may be seen within the context of an interrupted aortic arch. *Familial hypertrophic cardiomyopathy* is an autosomal dominant developmental abnormality most commonly due to mutations in the contractile protein (sarcomere) genes, but it may also be due to mutations in non-sarcomeric genes that are associated with mitochondrial defects, potassium channel abnormalities, and abnormalities of protein kinase A [70]. A *discrete fibromuscular ridge* or *membrane* below the aortic valve can also cause subaortic stenosis.

Congenital supravalvular aortic stenosis (SVAS) is caused by the deletion of or a loss-of-function mutation in the elastin gene on chromosome 7q11.23. In the majority of cases, SVAS occurs in association with Williams–Beuren syndrome, which is frequently referred to as Williams syndrome (WS) [71,72]. In other cases, SVAS is inherited as an autosomal dominant disorder or results from sporadic mutations and occurs without the mental retardation, elfin facies, distinctive behavioral traits, and neonatal hypocalcemia associated with WS [73]. During the early stages of development, the smooth muscle cells from patients with WS and non-syndromic SVAS express only about 15% and 50%, respectively, of the normal levels of the elastin-precursor tropoelastin [74]. The resultant arterial media has a reduced elastin content, pathologic alignment of the elastin fibers, an increased collagen content, and an increased number of hypertrophied smooth muscle cells. The entire ascending aorta may be narrowed (aortopathy) in about 30% of patients, and up to 80% of patients will have peripheral pulmonary artery stenosis [75].

KEY POINTS: CARDIAC SEPTATION

- Cardiac septation begins after the looping stage with eventual creation of four chambers and two distinct circulations.
- The process of cardiac septation involves the muscular septa in the atrial and ventricular chambers, the AV and outflow tract endocardial cushions, and the dorsal mesenchymal protrusion.
- Abnormalities in this process can result in septation defects at the atrial and/or ventricular levels, altered AV valve development, abnormalities of outflow tract septation, and semilunar valve pathology.

Epicardium and coronary artery development

After looping of the linear heart tube occurs, the epicardium covers the heart as well as the intrapericardial portion and roots of the great arteries. The epicardium is derived from two sources of extracardiac cells: the *proepicardial organ* (PEO) and the *splanchnic mesoderm of the ventral pharynx* (Figure 4.15) [23,76]. The venous PEO (vPEO) is derived from mesenchyme near or in the liver and begins as protrusions of splanchnic mesoderm at the venous pole at the back of the pericardial cavity. The vPEO gives rise to the epicardium that will cover the atria, AVC, and ventricles. Likewise, the splanchnic mesoderm of the ventral pharynx at the arterial pole, which is analogous to the PEO at the venous pole or vPEO, gives rise to the epicardium that will cover the outflow tract (arterial PEO or aPEO). Gittenberger-de Groot has shown that after the epicardium has invested the myocardium, a subset of cells undergoes endocardial-to-mesenchymal transformation and migrates into the subepicardial space [77]. These epicardially derived cells (EPDCs) invade the myocardium and endocardial cushions and undergo differentiation into fibroblasts, coronary smooth muscle cells, and endothelial and hematopoietic cells. The epicardially derived fibroblasts become the interstitial fibroblasts, the annulus fibrosus, and the adventitial coronary fibroblasts. The epicardium is necessary for myocardial growth, and interstitial fibroblasts are crucial to the formation of the thick compact myocardium.

Nutrient delivery to the myocardium occurs in three sequential and overlapping phases [47]. Although the early myocardium is avascular, the inner trabecular zone of the myocardial wall has venous sinusoids (trabecular channels) lined by endocardium through which nutrients diffuse. With the formation of the epicardium after cardiac looping, a subepicardial endothelial plexus forms from the EPDCs and undergoes vasculogenesis, angiogenesis, and arteriogenesis [78]. Arteriogenesis is the coating of the initial coronary plexus by smooth muscle cells and pericytes. The coronary plexus penetrates the myocardium, and some of the channels will communicate with the intratrabecular venous sinusoids. The density of the coronary plexus is not uniform across the myocardial wall, being higher on the outer epicardial side than on the inner endocardial side [76]. The subepicardial vascular network later undergoes remodeling to produce the coronary arteries and veins with adult branching characteristics. As reported by Gittenberger-de Groot et al. [78] and Waldo et al. [79], the final step in the development of the coronary circulation is ingrowth of the peritruncal coronary capillary plexus into the base of the aorta (Figure 4.16). Each coronary sinus has an ostium, which receives multiple small vessels. In the right and left aortic sinuses, the multiple channels coalesce to form the main stems of the right and left coronary arteries, whereas the channels in the remaining (non-coronary) sinus regress.

Abnormalities of epicardial development

Normal development of the compact myocardium requires a trophic interaction between the cardiomyocytes and EPDCs [23,80]. Abnormal EPDC function results in *ventricular non-compaction*, a cardiomyopathy that is characterized by a spongy myocardium and has a predilection for the left ventricle.

Coronary artery fistulae may arise from either the right or left coronary artery and most frequently terminate in the

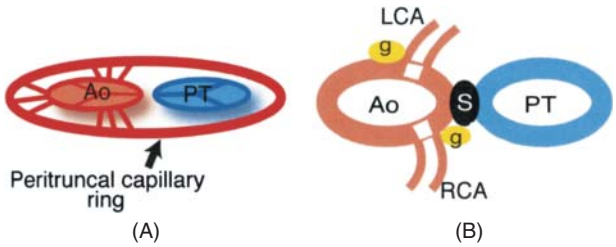


Figure 4.16 Left (LCA) and right (RCA) coronary artery development. (A) Multiple channels penetrate the aortic (Ao) wall in all of the aortic sinuses from the peritruncal ring. (B) Only the ones in the right and left sinuses survive and coalesce to form the main stems of the LCA and RCA. PT, pulmonary trunk; g, cardiac ganglia; S, aorticopulmonary septum. (Source: Waldo et al. [78]. Reproduced with permission of Wiley.)

right heart [81]. Fistulae can occur in isolation or in association with other lesions. In some cases of pulmonary atresia with intact ventricular septum (PA/IVS) and in some forms of HLHS [82], a significant portion of the ventricle may be dependent on blood supply from the hypertensive right (PA/IVS) or left ventricle, respectively. Flow into a lower pressure chamber produces myocardial ischemia by coronary steal and ventricular volume overload.

Vascular channels from the peritruncal ring normally penetrate the aortic sinuses [78]. However, penetration of the pulmonary artery results in an *anomalous origin of the coronary artery from the pulmonary artery*, the most common form being the left coronary artery arising from the pulmonary artery (ALCAPA) [83,84]. Coronary steal can occur, in which the blood flow is reversed into the pulmonary artery due to the lower vascular resistance of the pulmonary artery and/or the higher pressure of a collateral circulation from the normal coronary artery. Also, blood flowing antegrade through the anomalous coronary artery has a lower oxygen content than normal.

Congenital atresia of the left coronary artery and *anomalous aortic origin of the left or right coronary artery from the right or left coronary sinus*, respectively, are generally rare but have been associated with sudden death [83,84].

KEY POINTS: EPICARDIUM AND CORONARY ARTERY DEVELOPMENT

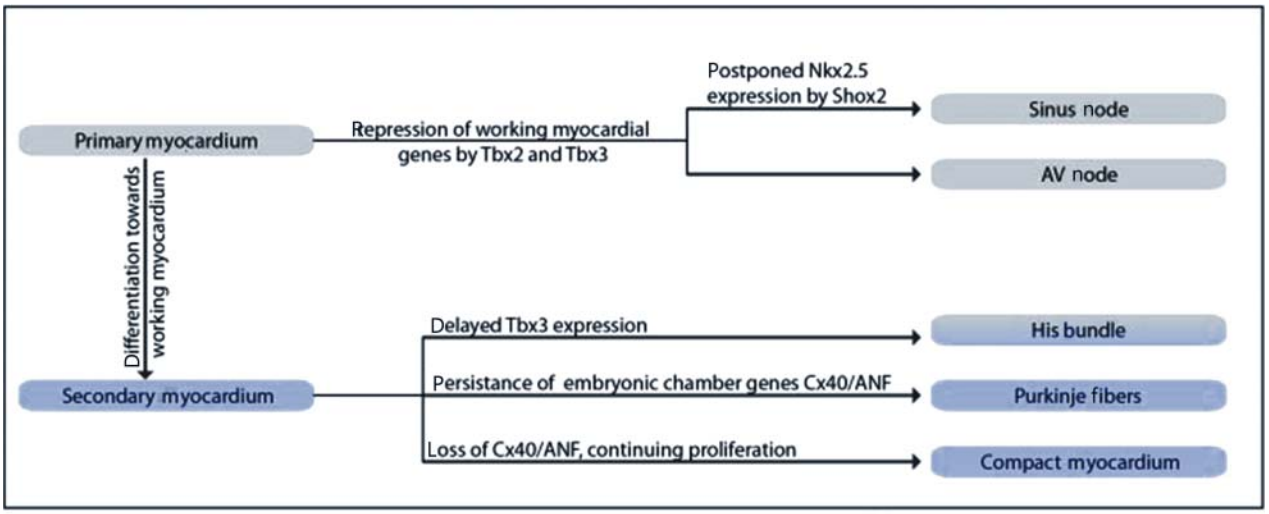
- The epicardium is derived from two sources of extracardiac cells.
- Epicardially derived cells undergo differentiation into fibroblasts, coronary smooth muscle cells, and endothelial and hematopoietic cells.
- The development of the coronary circulation involves various steps, the last one consisting of ingrowth of the peritruncal coronary capillary plexus into the base of the aorta.
- Abnormal epicardial development can result in certain types of cardiomyopathies and anomalies that involve the coronary arteries.

Development of the conduction system

The myocardium of the primitive heart tube has no morphologically distinct conducting cells [85,86]. The primitive pacemaker (i.e., area with the cells with the fastest intrinsic rate) is located at the junction of the sinus venosus and the primitive atrium. Before the AV and semilunar valves develop, a unidirectional, slowly transmitted, depolarizing impulse (represented by a sinusoidal electrocardiogram) generates a peristaltic contraction wave that pushes blood from the venous pole to the arterial pole. With elongation of the heart tube, the myocardial cells of the developing ventricular and atrial chambers differentiate into a working myocardial phenotype characterized by fast-conducting gap junctions and sarcomere components [87]. Myocardial cells at the venous pole, AVC, and outflow tract differentiate into specialized *conductive* myocardium. Although these cells have elements of working myocardium (including contraction, autorhythmicity, intercellular conduction, and electromechanical coupling), they retain their primary phenotype of sparse gap junctions and slow conduction (Figure 4.17) [87]. With differentiation of myocytes into working and conductive myocardium, the electrocardiogram resembles that of the formed heart [88].

The *sinoatrial node* (SAN) is detectable at approximately 32 days of gestation. It develops from myocardial cells located at the junction of the right common cardinal vein (which drains into the right horn of the sinus venosus) and the right atrium, ultimately becoming "comma-shaped" with its head at the junction of the SVC and the right atrium and its tail incorporated into the crista terminalis [89]. Nodal cells in the left cardinal vein regress to become the ligament of Marshall [85]. It has now been established that specific conduction pathways through the atrial myocardium do not exist [86,90]. The *AV node* (AVN) is detectable at approximately 33 days of gestation. It develops from slow-conducting myocardium within the dorsal AVC. The AVN becomes located in the triangle of Koch, and the cells of the AVN are in direct continuity with the atrial and ventricular myocardium. The AVN retains its primary phenotype of slow conduction so that there is appropriate AV delay. The *AV bundle*, *left and right bundle branches*, and *Purkinje fibers* develop from fast-conducting ventricular myocardium; the AV bundle from cells in the crest of the interventricular septum, and the bundle branches and Purkinje network from subendocardial myocytes along the ventricular septum [87].

An important step in the development of the conduction system is establishing electrical discontinuity between the atrial and ventricular myocardium at the AV junction. Epicardial cell-derived fibroblasts in the AV groove invade the AV myocardium inferior to the AVN and make contact with the endocardial cushion mesenchyme to form the *annulus fibrosus*, or crux of the heart. Because the annulus fibrosus insulates the atria from the ventricles, the AV conduction system provides the only myocardial continuity between the atria and ventricles.

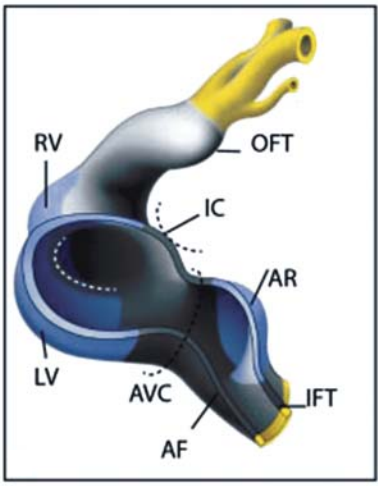


(A)

	Primary	Nodal	His bundle	Purkinje	Compact
Automaticity	High	High	High	Low	Low
Conduction velocity	Low	Low	High	High	High
Contractility	Low	Low	Low	Low	High

	IFT	AR	AF	AVC	IC	LV	RV	OFT
Tbx1	-	-	-	-	-	-	-	+
Tbx2	+	-	+	+	+	-	-	+
Tbx3	-	-	+	+	+	-	-	-
Tbx5	+	+	+	+	+	+	-	-
Tbx18	+	-	-	-	-	-	-	-
Tbx20	+	+	+	+	+	+	+	+

(B)



(C)

Figure 4.17 Differentiation of the primary myocardium. (A) Flow chart of the differentiation of primary and secondary myocardium into the different kinds of adult type myocardium. (B, upper table) Characteristics of different kinds of myocardium in terms of their contraction and electrophysiological behavior. (B, lower table) Summary of the expression pattern of different T-box transcription factors in different parts of the heart. Note that the primary myocardium always expresses either Tbx2, Tbx3, or both. (C) Schematic of the chamber-forming (ballooning) heart (gray, primary myocardium; blue, secondary myocardium). The gray area at the top of ventricular septum (white dotted line) retains characteristics of the primary myocardium and will become the atrioventricular bundle. AF, atrial floor; AR, atrial roof; AVC, atrioventricular canal; IC, inner curvature; IFT, inflow tract; LV, left ventricle; OFT, outflow tract; RV, right ventricle. (Source: Sylva et al. [24]. Reproduced with permission of Wiley.)

Abnormalities of conduction system development

Normal development of the conduction system is dependent upon concordance of the atrial and ventricular chambers, correct alignment of the atrial and ventricular septa, and complete closure of the ventricular septum [91]. Thus, from an embryologic perspective, abnormalities of the conduction system would be expected in lesions that involve AV concordance, the AVC, single ventricles, or combinations thereof.

Corrected TGA with L-loop ventricles is associated with displacement of the AVN to an anterior and lateral position within the right atrium; additionally, function of the AV conduction system is suboptimal and can result in spontaneous heart block [91]. In *CCTGA with D-loop ventricles and atrial situs inversus*, the AVN is typically in a left-sided triangle of Koch. In *AVC defects*, the AVN is displaced posteriorly to lie low in the atrial septum and anterior to the coronary sinus ostium. Likewise, the AV bundle is displaced posteriorly, is elongated, and courses along the lower rim of the VSD; this gives rise to the superior QRS axis seen on an electrocardiogram. With *perimembranous VSDs*, the AV bundle can be longer and is typically located along the postero-inferior rim of the defect. In *single ventricle* abnormalities, the locations of the AVN and AV bundle can vary widely.