Hanna K. **Gaggin**
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Editors

MGH CARDIOLOGY BOARD REVIEW

Second Edition

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Springer

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Foreword

It seems almost impossible to me that 7 years have elapsed since I wrote the foreword for the first edition of this invaluable cardiology board review book authored by Drs. Hanna Gaggin and James Januzzi Jr. Once again, I harken back to almost 60 years ago when I took my cardiovascular board examination. In retrospect, it seemed so simple then. The exams centered around the history, physical examination, ECG, x-rays, some primitive data from the cardiac catheterization laboratories, and the few medications we had to treat patients with heart disease. The amazing diagnostic techniques that exist today, e.g., echocardiography, CT and MRI scans, and many others, did not exist, nor did most of today's almost miraculous advances in the prevention and treatment of cardiovascular diseases. In fact, it was just about at that time that the avalanche of advances in the diagnosis and treatment of heart disease was just beginning and this continues to this day at what seems to be an ever-accelerating pace. Indeed, many advances have occurred since the first edition of this book. Parallel with these advances is a mountainous burden of new information that the cardiologist must try to assimilate.

Another consequence of this information explosion is that the specialty of cardiology has become increasingly compartmentalized into subspecialties. Whereas it was once possible for a cardiologist to be knowledgeable in the whole spectrum of cardiology, it is now all but impossible to keep track of the nuances that exist in many of the subspecialties, such as electrophysiology, congenital heart disease, and genetics. Yet there exists a body of knowledge within the specialty of cardiology that all cardiologists—including those in the subspecialties—are expected to possess. This is important not just for patient care, but also for teaching, which most board-certified cardiologists do in one form or another. That core body of knowledge is what the board examination seeks to define.

Getting ready for the board examinations requires the diligent and efficient use of those board preparation resources that are available. It is in this context that I am so enthusiastic about the publication of the second edition of the Massachusetts General Hospital (MGH) Cardiology Board Review Book by Drs. Gaggin and Januzzi of the MGH Division of Cardiology. Representing contributions from a broad array of the best and brightest from our division, this comprehensive review book has a concise, easy-to-read, visually appealing layout that will assist both those who are taking board examinations for the first time and those seeking recertification after many years of practice. The authors and editors take precautions not to overwhelm the reader with irrelevant information. Indeed, the contents of this book are designed to contain the most relevant in clinical practice and most often tested topics in each subject. The value of the book is further enhanced by the design of multiple-choice questions formulated by people who recently took the exam.

Finally, it gives me great pride to see the name of the MGH Cardiac Division on this book. Since the division was founded by Dr. Paul Dudley White in 1917, the MGH has enjoyed a rich tradition of excellence in the practice and teaching of clinical cardiology. Dr. White's single-authored textbook, *Heart Disease*, first published in 1931, was the definitive reference textbook in cardiology for 25 years. Subsequently, the MGH Cardiac Division published a highly acclaimed textbook *The Practice of Cardiology*. Many other books have

been published by members of the MGH Cardiac Division. The common denominator of these publications was that, for the most part, they were authored by cardiologists who actively took care of patients with heart disease. That is also true of this book's editors, Drs. Gaggin and Januzzi, as well as authors. This book is an important educational resource and the authors add further luster to the long tradition of the MGH for excellence in clinical teaching.

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Preface

It has been quite a journey! With a decade at Mass General under my belt, I cannot help but think of all those who made everything happen.

I am so thankful for my super mentor, colleague, and coeditor, Dr. James Januzzi. Jim brought me on as the Barry Fellow at Mass General 10 years ago and still continues to support my career growth in so many impactful ways. I love his dedication to his patients, his research team, his family, and all those in cardiology with his work through the American College of Cardiology and other organizations. Despite his superstar accomplishments, he somehow remains humble and available and always is willing to learn and grow. My research team whose work allows me to dig deeper into this wonderful field of cardiology. All the authors of this book who worked tirelessly, sometimes edits after edits, to make it of quality and of substance. It was my pleasure to have gotten to know them and their dedication to education through this book: Drs. Doug Drachman, Eric Isselbacher, Randy Zusman, Igor Palacios, Ik-Kyung Jang, Quynh Truong, Rory Weiner, and Aaron Baggish for their advice and for being the first brave ones to sign up for the first edition. Special thanks to Dr. G. William Dec who gave me my first faculty job at Mass General and supported my new ideas with his vision for the division. Drs. Tony Rosenzweig and Jag Singh for emboldening me to create and direct a live MGH Board Review Course and inspiring me to broaden my education experience to enduring content. The team at Harvard Medical School Postgraduate Medical Education for giving me the opportunity to direct its cardiology on demand course.

I really appreciate the wonderful network of colleagues at Mass General and Harvard Medical School who are unparalleled in their support of the education of medical students, residents, and fellows as well as peers.

I cannot thank enough Drs. Barry London, Mike Mathier and Rene Alvarez who entrusted me to create the Board Review Conference at the University of Pittsburgh Medical Center. Dr. John Gorcsan for opening my eyes to the art of presentation whose teachings on organization of material for learning I have used again and again. Too numerous to name, all the fellows and faculty members at the University of Pittsburgh Medical Center who contributed to the Board Review Conference.

I learned how to be a doctor from Dr. Robert Vorona, whose work ethics, character, and compassion I try to emulate each day. Dr. J. Catesby Ware whose leadership set the bar high for how to foster great research ideas and mentor trainees and junior faculty members at the Eastern Virginia Medical School.

On a personal note, I have to credit my mom, Hee Jung Kim, for making sure that I pursue what I love and for being the wisest, strongest woman I know. My sisters, Han Yount and Dr. Amy Pollak, for always being there for me. My very special angels, Ruth and Jim Clark—their sense of curiosity, adventure, and philanthropy were inspirational. My best friends, Drs. Ranjith Shetty and "Mattie" Matthew Campbell, for making sure that I appreciate life outside of work. Our Fav Eight, John and Amy Damask, Steve Marshall and Aileen Salares, Julia Shanks, and John Paskowski for always cooking and eating with us while keeping Rob and me sane.

But above all, I would like to thank my ultimate partner in crime and love Robert Gaggin and our three little wonderful kids. Thank you for all your support and love. Thank you most of all for always, even after a decade, making me laugh no matter how sleep deprived and tired I may be! I will work hard to make you proud!

Boston, MA Hanna K. Gaggin, MD, MPH, FACC

As the second edition of this text is coming to fruition, I am particularly reflective about what a blessing it is to be a mentor and sponsor for gifted, motivated individuals. It is incredibly rewarding when the mentee has a vision that exceeds that of the mentor. My coauthor Dr. Gaggin is a force of nature—a clinician, a clinical researcher, a teacher, a mother, a wife, and now a twice-published textbook author. Her vision, her drive, and her focus on the importance of teaching, education, and the need for this text are a testament to her maturity as an academic cardiologist. I could not be prouder and look forward to seeing her continued growth. I dedicate the efforts I put into this book to Dr. Gaggin.

To be able to do what I do for a quarter century and enjoy every minute has been a blessing. I am grateful to the Massachusetts General Hospital and Harvard Medical School for providing me the space to grow. My colleagues in the MGH Cardiology Division are without compare master clinicians and researchers extraordinaire.

I am so very grateful for the sacrifices my loving family has made to support me through my career—to my wife Roberta and daughters Caterina and Julianne: thank you, I love you, and I promise I will come home soon.

Lastly, to my colleagues interested in lifelong learning reading this book: thank you for your interest. The fact we are always learning as physicians is one of the best things about what we do. Happy studying, keep on growing, and nail the boards for me.

Boston, MA James L. Januzzi Jr., MD, FACC, FESC

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CHAPTER 1

HANNA K. GAGGIN AND JAMES L. JANUZZI JR.

How to Ace Cardiology and the Boards Including What to Review

CHAPTER OUTLINE

Whether you want a concise overview of cardiology or are studying for the initial/re-certification cardiovascular board exam, we have pooled the talents, the expertise and the teaching experience of the best and the brightest at Mass General to help you achieve your goal.

This book is not meant to be all-inclusive. There are several excellent, in-depth resources available such as UpToDate, ACCSAP, Braunwald's Heart Disease and Hurst's the Heart for that purpose.

This book is meant to be a primer for the highlights of cardiology topics (including board-style questions that test and consolidate your knowledge, electrocardiograms [ECG] and imaging studies for the busy clinicians, fellows, residents, medical students, nurse practitioners and specialty nurses.

The original inspiration for this book came from the board review conference created and run by Dr. Gaggin while at the University of Pittsburgh Medical Center and continues to be fueled by her education projects in books, live continuing medical education (CME) courses, on demand education programs with Mass General Hospital and Harvard Medical School as well as feedback from fellows and faculty members who recently took the exam. Dr. Januzzi is a frequent faculty member of board review courses and multiple clinical practice guideline committees and has won many teaching awards for his role in the education of trainees at Mass General.

Let's get started!

BASIC EXAMINATION INFORMATION

- **The exam is in the fall AFTER you finish your clinical cardiology fellowship (**check with your program if you are not on a typical 3-year clinical fellowship as the requirements are different).
- **When you start your last year of clinical cardiology fellowship, visit the official American Board of Internal Medicine (ABIM) website and obtain exact dates, cost (it's expensive, so you will need to plan ahead) and requirements as they change often:** (*http://www.abim.org*), *Become Certified* tab, *Exam Information* button at the bottom, and *Select an exam*, *Go*, select *Cardiovascular Disease.*
- **Key dates, *initial certification***
  - Register early—as soon as you know where you will be after the fellowship (registration typically opens up December 1 of your last year of fellowship)—in order to get your first choice in testing center.
    - Registration deadline: typically, June 15th of the last year of your fellowship
  - The examination is at the end of October/early November AFTER completing the clinical cardiology fellowship requirement.
  - If you must cancel, make sure to do it within the designated time (typically September 1st).

EXAM TIPS

Exam Format

- **Initial certification format**: 1½ days
- **Must pass both sections in order to pass the exam**.
  - Multiple choice questions (one full day)
    - four 2-h sessions, max 60 questions per one 2-h session, about 2.4 min/question.
  - ECG and imaging studies (½ day)
    - One 2 h-session, max 35 ECG's (about 3.4 min/ECG).
    - One 2 h and 15 min-session, max 37 imaging cases (71% echo and 29% coronary angiogram cases, about 3.6 min/case).
- **Maintenance of certification format**: One full day of multiple choice questions as above. No separate ECG or imaging section. The questions are pooled from the multiple choice questions used in the initial certification.

Multiple Choice Questions

- Review the *Cardiovascular Disease Certification exam blueprint* on ABIM website as they follow this when creating the exam. It also lists specific disorders that may be included. **Make sure that you know all of these disorders (diagnosis and management) at the minimum as test questions are made from this blueprint.**

MEDICAL CONTENT CATEGORY	% OF EXAM
Arrhythmias	15
Coronary artery disease	23
Heart failure and cardiomyopathy	17
Valvular disease	15

MEDICAL CONTENT CATEGORY	% OF EXAM
Pericardial disease	4
Congenital heart disease	5
Vascular disease	6
Systemic hypertension and hypotension	7
Pulmonary circulation disorders	5
Systemic disorders affecting the circulatory system	3

They also point out the following clinical topics are embedded in the above blueprint:

- Preventive and rehabilitative cardiology
- Cardiovascular disease in women
- Geriatric cardiovascular disease
- Preoperative assessment for noncardiac surgery
- Postoperative cardiac care
- Critical care medicine, cardiovascular surgery, and general internal medicine as encountered in the practice of cardiology (including some general pediatrics with an emphasis on adolescent medicine)

- You will be expected to interpret ECG's, intracardiac electrograms, hemodynamic recordings, chest radiographs, photomicrographs, and imaging studies such as coronary angiograms, echocardiograms, ventriculograms, myocardial perfusion studies, computed tomograms, magnetic resonance images, and intravascular ultrasound images. Some questions may also require recognition and interpretation of recorded heart sounds but this has not been in all the exams since it was first introduced as a possibility.
- Know your weaknesses. Expect that there will be questions in that area. There is nothing more satisfying than correctly answering questions in a prior area of weakness!
- While there are no guarantees, there are certain things you can well-expect on the examination:
  - **You must know the latest American College of Cardiology (ACC)/American Heart Association (AHA) Clinical Practice Guideline recommendations.**
    - **There is <u>heavy</u> emphasis on Class I recommendations (what to do) and Class III recommendations (what not to do). If there is controversy about a topic, it will not be tested.**
    - If there is a new publication of practice guidelines, go with what you know is the updated standard of care; ABIM will decide if that question should count or not after the test results are analyzed.
  - **Good, old fashioned clinical evaluation is emphasized on the exam: know your history and physical (see Chapter 1 of this text), and know how the findings on history and physical tie in to management.**
- Don't be discouraged by questions that seem out of nowhere. About 10% of the questions are new questions that are being explored for use and do not count toward your score.
- Get used to board-style exam questions, they are long-winded, and often have an extended "stem" that can mis-lead you from the real reason for the question.
  - More than 75% of questions are based on patient presentations, with the majority requiring integrating numerous aspects of the data presented—but not all of it!
    - Our advice is to read the question and the answers list first, then circle back to read the long description of the situation.
- **There is no penalty for guessing, so do not leave any questions unanswered! Pick your favorite alphabet letter and go with it if you run out of time.**
- Sorry, no UpToDate access for initial exam takers!

ECG Section (Only for the Initial Exam)

- **We cannot emphasize how important it is to KNOW THE ANSWER OPTIONS LIST BY HEART that ABIM provides on its website, tutorial and Sample cases.**
  - Check out the ***Tutorial*** and download the **Sample Cases** (from Cardiovascular Disease Certification Exam, check Content tab, open the link to *ECG and Imaging Studies component of the exam (pdf)* in blue, page 10 under Exam format, click on the blue link to *Sample Cases-Electrocardiograms and Imaging Studies (pdf)*). Samples cases will have answers to samples cases and **PAY SPECIAL ATTENTION TO *SCORING OF SAMPLE CASES*** as they provide priceless insight into the way ABIM will score your ECG's and imaging studies.
  - **Know the answer options list by heart** (how many times can we say this?), so you can rapidly find the diagnoses you seek and know these diagnosis by heart.
- **Format**: Most people fail the board exam because they failed the ECG section. **The most frequent comment was that they ran out of time, usually because they wasted too much time looking for the location of the answer in the answer options list.**
- **You DO get penalized for overcoding or guessing** in this section, so code only what you need.

Imaging Studies Section (Only for the Initial Exam)

- **Similar to the ECG section. Know the Answer options list and Samples Cases for how they score.**
- **You DO get penalized for overcoding** or guessing in this section, so code only what you need.

WHAT TO REVIEW: A CHECK LIST FOR INITIAL TEST-TAKERS

When You Have 6–12 Months: A Check List for Initial Test-Takers

- General Study materials
  - Start with the ***MGH Cardiology Board Review book*** to get an overview first and identify areas of weakness.
  - **Go over ABIM's exam expanded blueprint that contains all the disorders that you can be tested on** and make sure that you focus on clinical diagnosis and management (including screening, monitoring and treatment).
  - Review all the available/latest **ACC/AHA guidelines**-especially Class I and III recommendations
  - Review all the disorders in ***UpToDate***. Becoming familiar using UpToDate may come handy in the future as you will have access to UpToDate on re-certification exams and Knowledge Check in's if you choose those options.
  - **If you come across a useful slide, table or a figure that you find useful, take a picture of it and save it to a folder for review during the week or month before the test**
  - While you may or may not get tested on heart sounds on the multiple choice questions section, ACC/CardioSource's ***Heart Songs*** is an excellent place to review and learn heart sounds. Some of the digital stethoscope companies give you access to heart sounds but not sure how accurate they are.
  - Optional: Mayo Clinic's *General Cardiovascular Board Review* online course with videos of the live course, multiple choice questions and select ECG/echo/cath cases with scoring, may speed up the talks at ×1.5 speed to save time, expensive, a great course but mixed reviews on how helpful for the boards

- Multiple choice questions
  - Plan on covering all of ***ACCSAP*** **questions and answers** (Essential for the well-written, accurate practice exam questions. Very similar to the actual ABIM question format).
- ECG
  - Start with the **ABIM Answer Options List and Sample Cases** with scoring as these are the only answer options (all the diagnoses that they can test you on)
    - Print the **ABIM's Answer Options List** (can be found in the Sample Cases pdf) and practice filling it out
  - The gold standard is ***The Complete Guide to ECG's*** **by James O'Keefe**. Do the book and know *ECG Criteria* section by heart. Pay attention to those that are on the ABIM Answer Options List.
  - ***ECG*** **chapter from the** ***MGH Cardiology Board Review Book*** that includes almost all the diagnosis from the ABIM Answer Options list
  - *Optional: Podrid's Real World ECG's*. Start with Volume 1, The Basics. **Great ECGs, detailed explanations with review of criteria and differential diagnosis embedded in a clinical situation.** However, you may have to order the book directly from the publisher. While this is a great ECG book in general, for the board preparation, you may want to look at the index to look for the ABIM Answer options list diagnoses and review those ECG's first.
  - *Optional: ECGSource* website has ECGs with scoring, some internal inconsistencies though
  - *Optional: ECG Drill and Practice (formerly known as ECGSAP)* from ACC/CardioSource from ACC (its scoring system gives you an insight to the way ABIM will score, especially for the penalties for overcoding a diagnosis, but the scoring system is a little different from ABIM)
- Imaging Studies section
  - As above, know all the diagnoses in the **ABIM Answer Options List** and review **Sample Cases** with scoring
    - Print the **ABIM's Answer Options List** (can be found in the Sample Cases pdf) and practice filling it out
  - *Imaging* chapter of the ***MGH Cardiology Board Review Book*** that includes almost all the diagnosis from the ABIM Answer Options list.
  - *Review ABIM's Answer Options List diagnoses from echo books such as* ***Textbook of Clinical Echocardiography by Dr. Otto*** and their ***videos***
  - ***ECGSource*** website, most useful for cath and echo cases and scoring practice but some internal inconsistencies.
  - *Optional: EchoSAP* from CardioSource, similar to ECGSAP from ACC, slightly different coding system, expensive though.

What to Review When You Have 3 Months

- General Study materials
  - Start with the ***MGH Cardiology Board Review book*** to get an overview first and identify areas of weakness.
  - **Go over ABIM's exam expanded blueprint that contains all the disorders that you can be tested on** and make sure that you focus on clinical diagnosis and management (including screening, monitoring and treatment).
  - Review all the available/latest **ACC/AHA guidelines**-especially Class I and III recommendations. Focus on figures and tables.

  - Review all the disorders that you need to brush up in ***UpToDate***. Becoming familiar using UpToDate may come handy in the future as you will have access to UpToDate on re-certification exams and Knowledge Check in's if you choose those options.
  - **If you come across a useful slide, table or a figure that you find useful, take a picture of it and save it to a folder for review during the week before the test**

- Multiple choice questions
  - Plan on covering all of ***ACCSAP*** **questions and answers** (Essential for the well-written, accurate practice exam questions. Very similar to the actual ABIM question format).

- ECG
  - Start with the **ABIM Answer Options List and Sample Cases** with scoring as these are the only answer options (all the diagnoses that they can test you on)
    - Print the **ABIM's Answer Options List** (can be found in the Sample Cases pdf) and practice filling it out
  - The gold standard is ***The Complete Guide to ECG's*** **by James O'Keefe**. Do the book and know *ECG Criteria* section by heart. Pay attention to those that are on the ABIM Answer Options List.
  - ***ECG*** **chapter from the** ***MGH Cardiology Board Review Book*** that includes almost all the diagnosis from the ABIM Answer Options list

- Imaging Studies section
  - As above, know all the diagnoses in the **ABIM Answer Options List** and review **Sample Cases** with scoring
    - Print the **ABIM's Answer Options List** (can be found in the Sample Cases pdf) and practice filling it out
  - *Imaging* chapter of the ***MGH Cardiology Board Review Book*** that includes almost all the diagnosis from the ABIM Answer Options list.
  - ***ECGSource*** website, most useful for cath and echo cases and scoring practice but some internal inconsistencies.
  - *Review ABIM's Answer Options List diagnoses from echo books such as* ***Textbook of Clinical Echocardiography by Dr. Otto*** and their ***videos***

What to Review When You Have 1 Month

- **If you come across a useful slide, table or a figure that you find useful, take a picture of it and save it to a folder for review during the week before the test**
- Start with the ***MGH Cardiology Board Review book*** to get an overview first
- Review ABIM's expanded blueprint of specific disorders that they will test you on
  - Pick out and review specific topics that you need to brush up on first with **ACC/AHA guidelines Class I and III recommendations (focus on Tables and Figures) and UpToDate**

- For the ECG and Imaging sections:
  - Print the **ABIM's Answer Options List** (can be found in the Sample Cases pdf)
  - Know the diagnostic criteria for all the diagnoses covered in the **ABIM's Answer Options List and Sample Cases** with scoring from ABIM website as these are the only answer options (all the diagnoses that they can test you on).
    - Know all the ***ECG Criteria*** for the diagnoses listed in the ABIM's Answer Options List in the ***MGH Cardiology Board Review*** book and ***The Complete Guide to ECG's*** **by James O'Keefe**.
    - Review the ECG's from above with diagnoses listed in the ABIM's Answer Option List.

- Try to cover as many of ***ACCSAP*** **questions and answers** as you can; getting into the groove of test taking is important at this stage.
- Optional: ***ECGSource*** website, most useful for cath and echo cases and scoring practice but some internal inconsistencies
- *Review ABIM's Answer Options List diagnoses from echo books such as* ***Textbook of Clinical Echocardiography by Dr. Otto*** and their ***videos***

WHEN YOU ARE RE-CERTIFYING

Cardiovascular board re-certification and maintenance of certification is continuously evolving. There are now three options starting in 2019: ACC website has a nice summary of your MOC requirements including links to the three options. https://www.acc.org/education-and-meetings/maintenance-of-certification-information-hub

- Subspecialists certified in 1990 or later must complete the Maintenance of Certification (MOC) program, which includes 100 MOC points of self-evaluation every 10 years, with at least one activity every 2 years.
- In addition, you have to pass one of the following three options: a re-certification exam, Knowledge Check In or Collaborative Maintenance Pathway with ACC.

	FREQUENCY	OPEN BOOK?	LOCATION	CAVEATS
1 Traditional re-certification exam	Every 10 years	Yes: access to UpToDate	Test centers, proctored	Test offered twice a year
2 Knowledge Check In (New in 2019)	Every 2 years	Yes: access to UpToDate	Test centers or Home or Office, uninterrupted and semi-proctored	Test offered twice a year. If your certification lapses in 2020, you can/should take it in 2019 in General Cardiology.
3 Collaborative Maintenance Pathway with American College of Cardiology (New in 2019)	Every 1 year	Yes: access to ACCSAP	Anywhere with online access to ACCSAP, not proctored	Assessment available as two 1-week windows in Fall 2019. Have to purchase access to ACCSAP every 5 years. Also get CME/MOC points for the time engaged.

That's it—happy studying, and we wish you all the best!

CHAPTER 2

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History and Physical Examination

CHAPTER OUTLINE

ABBREVIATIONS

ACS	Acute coronary syndrome
AR	Aortic regurgitation
AS	Aortic stenosis
ASD	Atrial septal defect
AV	Aortic valve
CMP	Cardiomyopathy
CP	Chest pain
GERD	Gastroesophageal reflux disease
HCM	Hypertrophic cardiomyopathy
HTN	Hypertension
JVP	Jugular venous pressure
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
LV	Left ventricle
LVOT	Left ventricular outflow track
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MR	Mitral regurgitation
MS	Mitral stenosis
MV	Mitral valve
MVP	Mitral valve prolapse
PA	Pulmonary artery
PAD	Peripheral arterial disease
PDA	Patent ductus arteriosus
PE	Pulmonary embolism
PH	Pulmonary hypertension
PMI	Point of maximal impulse
PP	Pulse pressure
PR	Pulmonic regurgitation
PS	Pulmonic stenosis
PTX	Pneumothorax
PV	Pulmonic valve
PVC	Premature ventricular complex

RBBB	Right bundle branch block
RV	Right ventricle
RVH	Right ventricular hypertrophy
SOB	Shortness of breath
TOF	Tetralogy of Fallot
TR	Tricuspid regurgitation
TS	Tricuspid stenosis
TV	Tricuspid valve
VSD	Ventricular septal defect
WPW	Wolff-Parkinson-White

HISTORY

General History

The general history is the **subjective** portion of the patient interview and is comprised of the following sections (in order):

Chief complaint

- **Common presenting cardiovascular symptoms include**: chest pain (CP), shortness of breath (SOB) or dyspnea, edema, palpitations, dizziness, syncope, fatigue, weakness (see section "Approach to Common Chief Complaints" for more)
- **Chief complaints in asymptomatic patients**: abnormal imaging findings, pre-operative evaluation, cardiac screening before participation in sports

History of present illness

- Use **BOLDCARTS** mnemonic to describe presenting illness: before, onset, location, duration, characteristics, aggravating/alleviating factors, radiation, timing, severity
- Each HPI should begin with a discussion of the patient's **baseline functionality** (including exercise capacity) and **relevant past medical history** [1]

Past medical history

- Important cardiovascular past medical history to discuss include:
  - Traditional cardiovascular risk factors (hypertension, hyperlipidemia, metabolic syndrome, diabetes mellitus, smoking status, obesity, exercise)
  - Vascular disorders (peripheral arterial disease [PAD], stroke)
  - Co-existent pulmonary disease: chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA)
  - Prior chest surgery, radiation therapy, cardiotoxic medications

Medications

- Cardiac medications, relevant non-cardiac medications (e.g., phosphodiesterase inhibitors taken for erectile dysfunction), herbal supplements
- Compliance with medication regimen

Allergies

- Document all drug allergies and intolerances (including iodinated contrast)

Social history

- **Personal information**: place of birth/nationality, current living situation, occupation, family (spouse, children, siblings)
- **Habits**: tobacco products (cigarettes, electronic cigarettes, cigars, chewing tobacco), alcohol, illicit drugs (e.g., cocaine, marijuana, amphetamines, heroin)
- **Sexual history**: history of sexually transmitted diseases (e.g., syphilis, HIV)

Family history

- **Screen for family history of**: premature coronary artery disease (<65 years old in men, <55 years old in women), hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmias, sudden cardiac death, connective tissue disorders (e.g., Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome)

Review of systems

- Neurologic, pulmonary, gastrointestinal, urinary, infectious, hematologic, immunologic, musculoskeletal, endocrine, and psychiatric systems should be reviewed

Approach to Common Chief Complaints

Chest pain (CP) (Tables 2-1 and 2-2)

- **Typical angina** [2]: exertional or stress-related, substernal discomfort, resolves with rest or nitroglycerin; response to nitroglycerin in the emergency department is not predictive of cardiac etiology [3]
  - **Anginal equivalents**: retrospective study of 721 patients with acute myocardial infarction in the emergency department demonstrates a wide array of symptoms upon initial presentation [4]
    - Chest, left arm, jaw, or neck pain (53%), SOB (17%), cardiac arrest (7%), dizziness/weakness/syncope (4%), abdominal complaints (2%), miscellaneous (trauma, gastrointestinal bleeding, altered mental status, nausea/vomiting, palpitations, and others) (17%)
    - Atypical presentation is associated with an increased risk of adverse outcomes and more common in **women, elderly, and patients with diabetes mellitus** [5, 6]
- **Pericarditis:** abrupt onset, sharp, pleuritic, positional (improves with sitting forward and worsens with lying down), radiates to back, often preceded by recent fever or viral illness

TABLE 2-1

CHEST PAIN CHARACTERISTICS AND LIKELIHOOD RATIO FOR ACUTE CORONARY SYNDROME [7]

INCREASED LIKELIHOOD	LR (95% CI)	DECREASED LIKELIHOOD	LR (95% CI)
Radiates to right arm or shoulder	4.7 (1.9–12)	Pleuritic	0.2 (0.1–0.3)
Radiates to both arms or shoulders	4.1 (2.5–6.5)	Sharp	0.3 (0.2–0.5)
Precipitated by exertion	2.4 (1.5–3.8)	Positional	0.3 (0.2–0.5)
Radiates to the left arm	2.3 (1.7–3.1)	Reproducible with palpation	0.3 (0.2–0.4)
Associated with diaphoresis	2.0 (1.9–2.2)		

ACS acute coronary syndrome, *CI* confidence interval, *CP* chest pain, *LR* likelihood ratio

TABLE 2-2

DIFFERENTIAL DIAGNOSIS FOR CHEST PAIN

Cardiac: Acute coronary syndrome (ACS), aortic dissection, valvular heart disease, congestive heart failure (CHF), myocarditis, pericarditis, variant (Prinzmetal) angina, myocardial infarction with non-obstructive coronary arteries (MINOCA), cocaine use, stress-induced cardiomyopathy
Pulmonary: PE, pleuritis, pneumonia, pneumothorax, reactive air way disease, pulmonary hypertension, malignancy, sarcoidosis, pleural effusion, mediastinitis
Gastrointestinal: GERD, esophageal spasm, esophageal tear or rupture, esophagitis, peptic ulcer disease, cholecystitis, biliary colic, pancreatitis, kidney stones
Musculoskeletal: costochondritis, spinal disease, fracture, muscle strain, herpes zoster
Psychogenic: anxiety, panic disorder, depression, hypochondriasis

  - Often associated with **pericardial effusion** (muffled or distant heart sounds) and/or **tamponade** (distant heart sounds, hypotension, jugular venous distension (JVD), dyspnea, tachycardia, pulsus paradoxus) [8]
  - **Constrictive pericarditis**: associated with history of chest radiation, cardiac or mediastinal surgery, chronic tuberculosis, and malignancy; consider if patient presents with **pleuritic CP plus right-sided heart failure signs/symptoms**

- **Aortic dissection:** abrupt onset (85%), chest pain (61%, usually sharp or tearing), back pain (53%), abdominal pain (30%) [9]
  - **Triad of**: (1) sudden, severe, tearing CP with radiation to the back; (2) unequal arm blood pressure (BP) >20 mmHg; and (3) wide mediastinum on CXR has a positive likelihood ratio of 66.0 (CI 4.1–1062-0) for acute aortic dissection [10]
  - Extension into ascending aorta/aortic arch may cause **hemopericardium (tamponade)** and/or **aortic regurgitation**
  - **Occlusion of aortic branch vessels** may lead to diverse additional symptoms, including: neurologic deficits/stroke (carotid), pulse deficit (subclavian), acute mesenteric ischemia (celiac/SMA/IMA), renal infarction (renal), acute limb ischemia (subclavian, iliac)
  - **Association with blood pressure** [9]:
    - Thoracic aortic dissection: may present with hypertension (36%), normotension (40%), or hypotension/shock (25%)
    - Descending aortic dissection: patients usually hypertensive (49%); hypotension/shock rare (16%)
  - **Associated conditions**: aortic coarctation, bicuspid aortic valve, Marfan syndrome, Ehlers-Danlos syndrome, Turner syndrome, giant cell arteritis, pregnancy (third trimester), cocaine abuse, trauma, iatrogenic injury from endovascular catheterization, prior cardiac surgery

- **Other acute intra-thoracic pathology**:
  - **Acute pulmonary embolism (PE)**: sudden onset, pleuritic, dyspnea, tachycardia, tachypnea, hemoptysis, hypoxemia, evidence of lower extremity deep venous thrombosis
  - **Tension pneumothorax**: sudden onset, sharp, pleuritic, decreased breath sounds and chest excursion, tracheal deviation away from affected side, hyper-resonant to percussion, hypoxemia
  - **Esophageal rupture/perforation**: severe, increases with swallowing, fever, abdominal pain, history of endoscopy/foreign body ingestion/trauma/vomiting, new-onset left pleural effusion, pneumomediastinum, subcutaneous emphysema

Palpitations [11]

- Often described as: flutters, skipping, pounding sensation, heart "turning over" in chest
- History of cardiac disease increases the likelihood for cardiac arrhythmia (likelihood ratio [LR] 2-0, 95% confidence interval [CI] 1.3–3.1)
- Palpitations associated with a regular, rapid pounding sensation in the neck are strongly predictive of atrioventricular nodal re-entry tachycardia (LR 177, 95% CI 25–1251)
- May terminate with **vagal maneuvers** (carotid sinus massage, Valsalva maneuver, knees tucked into chest, cough, forced gag, cold stimulus to face)

Dyspnea

- **Differential diagnosis**: cardiac, pulmonary, neuromuscular, anemia, psychiatric, other (e.g., deconditioning, obesity)
- **Cardiac causes**:
  - **Heart failure**: may be either primary or secondary to other cardiovascular disorders; symptoms caused by:
    - Lack of adequate forward flow: fatigue, weakness, exercise intolerance
    - Increased left-sided filling pressures: dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND)
    - Increased right-sided filling pressures: right upper quadrant pain (hepatic congestion), ascites, peripheral edema
  - **ACS:** typically presents with dyspnea on exertion (see "**chest pain**" above)
  - **Pericarditis/pericardial effusion:** see "**pericarditis**" above

Claudication [12, 13]

- **Types of claudication**:
  - **Classic**: exertional calf pain that resolves with rest, prevents patient from walking
  - **Atypical**: pain that either does not involve the calf, does not resolve with rest, or does not prevent the patient from walking (usually occurs in the presence of concomitant diabetes, neuropathy, or spinal stenosis)
  - In new outpatients diagnosed with PAD, 47% did not have claudication, 47% had atypical claudication, and only 6% had classic claudication [13]
- **Associated physical exam findings**:
  - Dry/shiny/hairless skin, cool extremities, pallor with limb elevation, rubor with limb in dependent position, diminished pulses and sensation, distal digit ulceration, gangrene (dry/wet)
  - Location of the pain depends on the level of arterial narrowing (Table 2-3)
  - History can help differentiate between vascular and neurogenic claudication (Table 2-4)

TABLE 2-3

CORRELATION BETWEEN THE SITE OF PAIN AND THE LOCATION OF ARTERIAL STENOSIS

LOCATION OF PAIN	ANATOMIC LOCATION
Buttock/hip	Aortoiliac
Thigh	Aortoiliac or common femoral
Upper 2/3 of calf	Superficial femoral
Lower 1/3 of calf	Popliteal
Foot	Tibial or peroneal

TABLE 2-4

DIFFERENTIATION BETWEEN VASCULAR AND NEUROGENIC CLAUDICATION

	NEUROGENIC	VASCULAR
Increased with walking	Yes	Yes
Relieved with back flexed	Yes	No
Relieved sitting/lying down	Within minutes	Immediately
Increased with walking uphill/up stairs	No	Yes
Increased with walking downhill/down stairs	Yes	No

PHYSICAL EXAMINATION

General Examination

Vital signs

- **Significant difference in pulses and/or BP between both arms (SBP > 20 mmHg)**: aortic coarctation (R > L), aortic dissection (R > L), subclavian stenosis (R > L or L > R), supravalvular aortic stenosis (R > L; due to high-velocity jet that is preferentially directed toward the right aortic wall) [14]
- **Significant difference in the pulses and/or BP between arms and legs (SBP > 20 mmHg)**: severe aortic regurgitation (Hill sign; LE > UE), aortic coarctation (UE > LE), calcific lower extremity PAD (UE > LE), Takayasu/giant cell arteritis (UE > LE)
  - Note: **brachiofemoral pulse delay** is specific for aortic coarctation
- **Pulse pressure (PP)**: PP = SBP − DBP
  - Wide PP: aortic regurgitation, older age, severe atherosclerosis
  - Narrow PP: severe aortic stenosis, tamponade, hypertrophic cardiomyopathy (HCM), severe heart failure/cardiogenic shock (PP < 25% is associated with cardiac index <2.2 L/min/m^2) [15]
- **Orthostatic blood pressure**: defined as drop in SBP > 20 mmHg or DBP > 10 mmHg within 3 min of standing [16]
  - Note: heart rate response is **NOT** included in the definition of orthostatic BP, but increase in heart rate >30 beats per minute upon standing is highly suggestive
- **Valsalva response** (Fig. 2-1)
  - **Normal**: sinusoidal response
    - Phase 1 (initiation): acute rise in SBP occurs at the initiation of the Valsalva maneuver (VM) → Korotkoff sounds become **present**
    - Phase 2 (maintenance): as the VM is maintained, a gradual decrease in SBP occurs due to ↓ cardiac output (↓ venous return, ↑systemic vascular resistance)→ Korotkoff sounds **disappear**
    - Phase 3 (termination): VM is terminated and SBP acutely drops→ Korotkoff sounds **remain absent**
    - Phase 4 (overshoot): following the termination of the VM, there is a secondary rise in SBP due to a reflexive sympathetic surge triggered by the acute drop in SBP during Phase 3 → Korotkoff sounds **reappear**
  - **Heart failure**: two patterns of the Valsalva response are seen in heart failure
    - Absent overshoot: phase 4 overshoot does not occur, so the Korotkoff sounds **do not reappear**
    - Square wave: Korotkoff sounds are **present** throughout the phase 2 maintenance of the Valsalva maneuver AND phase 4 overshoot does not occur (Korotkoff sounds **do not reappear**)
    - Clinical correlation:
- Study of 81 patients demonstrated significant difference in left ventricular ejection fraction between patients with sinusoidal response (LVEF 55% ± 15%), absent overshoot (LVEF 37% ± 18%), and square wave (LVEF 16% ± 4%) [17]
- Square wave response has 93% specificity for LVEF < 40% [18]

Skin

- Evidence of poor perfusion (cold/clammy skin, poor capillary refill), cyanosis (congenital heart disease, shunts), skin bronzing (hemochromatosis), ecchymoses (antiplatelet or anticoagulation medication), xanthoma (subcutaneous lipid nodule), xanthelasma (xanthoma on eyelid), digital ulcer/gangrene

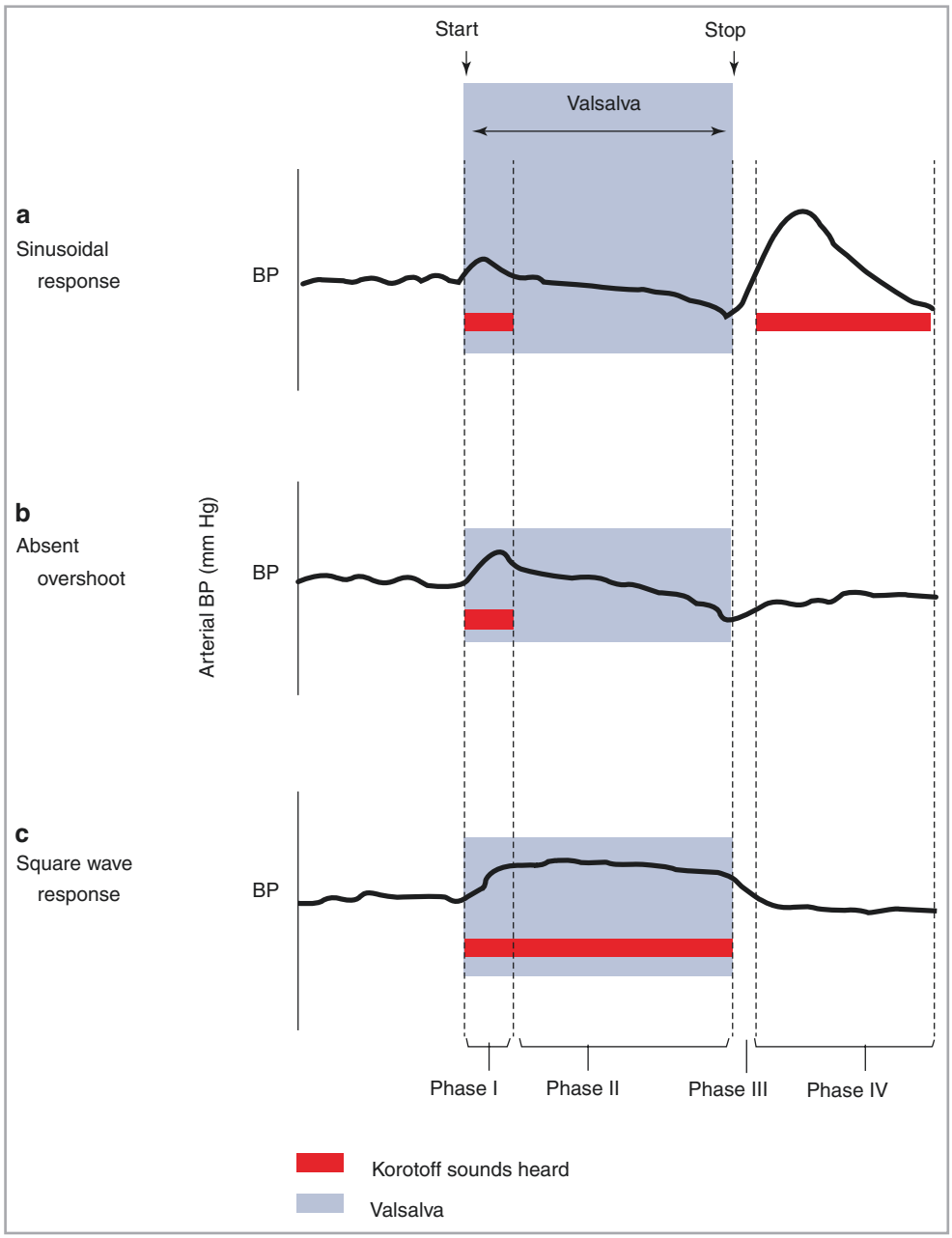


FIGURE 2-1

Normal and abnormal Valsalva responses. The gray box indicates when the Valsalva maneuver is performed. The red line indicates when Korotkoff sounds are heard. (**a**) Sinusoidal response in normal patient. (**b**) Absent overshoot in patient with mild to moderate heart failure. (**c**) Square wave response in patient with severe heart failure [19]

1 cm H_2O = 0.74 mmHg
1 mmHg = 1.36 cm H_2O

FIGURE 2-2

Conversion between mmHg and cm H_2O

Head and neck

- Elevated jugular venous pressure (CHF), high arched palate (Marfan), glossitis (amyloidosis), ptosis and ophthalmoplegia (muscular dystrophy), webbed neck (Turner syndrome) proptosis/lid lag (hyperthyroidism), split uvula (Loeys-Dietz syndrome)
- **Jugular venous pressure (JVP)**
  - Calculation of JVP in mmHg:
    - 1. Determine the vertical distance from the sternal angle to the top of the venous pulsation (in cm H_2O)
    - 2. Add 5 cm if bed incline is at 0–45° or 10 cm if bed incline is at >45° [20]
    - 3. Divide by 1.36 to convert to mmHg (Fig. 2-2)

- Normal JVP: ≤8 mmHg
- Clinical correlation: clinical assessment of the presence of an elevated JVP (rather than an exact numerical measurement of JVP) is accurate in predicting elevated right atrial (RA) pressure and pulmonary capillary wedge pressure (PCWP)
  - JVP < 11 cm predicts invasively measured RA pressure <8 mmHg with negative predictive value = 82% [21]
  - Presence of elevated JVP at rest or hepatojugular reflux in predicting PCWP > 18 mmHg: sensitivity = 81%, specificity = 80%, predictive accuracy = 81% (if measured in the absence of cirrhosis, volume overload from renal disease, and right-sided cardiac disease) [22]

■ **Jugular (central) venous pressure waveforms** (Table 2-5)

TABLE 2-5

ABNORMAL JUGULAR VENOUS PRESSURE WAVEFORMS

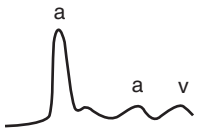
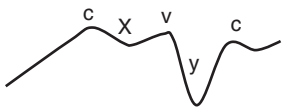
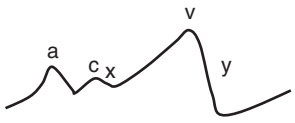
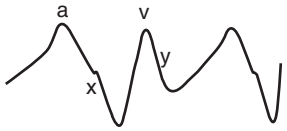
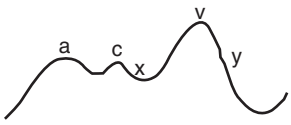
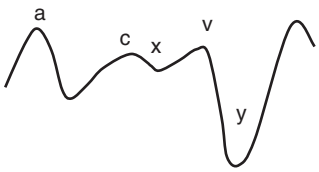
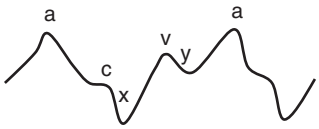
TRACING	PATHOPHYSIOLOGY
Prominent a wave 	Cause: Impaired RA emptying during atrial systole ■ Right atrial thrombus or mass (myxoma) ■ Tricuspid stenosis ■ Increased RV pressure: pulmonary hypertension (PH), severe RV hypertrophy, pulmonic stenosis
Cannon a wave 	Cause: RA contraction against a closed tricuspid valve ■ AV dissociation (complete heart block, ventricular tachycardia) ■ Premature beats (atrial, junctional, ventricular)
Absent a wave 	Cause: lack of effective RA contraction ■ Atrial fibrillation ■ Sinus arrest ■ Ebstein's anomaly
Equal a wave and v wave 	Cause: increased RA filling during LV systole ■ ASD (if PH is present)
Prominent v wave 	Cause: increased RA filling during LV systole ■ Tricuspid regurgitation ■ ASD (if PH is absent)
Prominent x descent 	Cause: rapid RA relaxation during LV systole ■ Tamponade (early finding) ■ Constrictive pericarditis

TABLE 2-5

(CONTINUED)

TRACING	PATHOPHYSIOLOGY
Blunted x descent 	Cause: decreased RA relaxation during LV systole ■ Tricuspid regurgitation ■ ASD ■ Restrictive cardiomyopathy
Prominent y descent 	Cause: rapid RA emptying during LV diastole ■ Constrictive pericarditis ■ Restrictive cardiomyopathy ■ Tricuspid regurgitation ■ Atrial septal defect
Blunted y descent 	Cause: impaired RA emptying during LV diastole ■ Tamponade (late finding) ■ Tricuspid stenosis ■ Right atrial thrombus or mass (myxoma) ■ Increased RV pressure: pulmonary hypertension (PH), severe RV hypertrophy, pulmonic stenosis

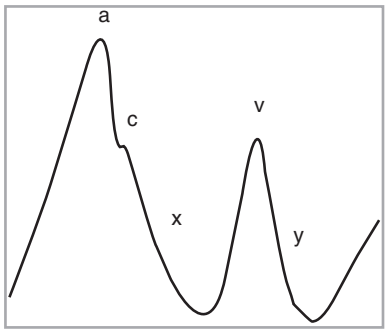


FIGURE 2-3

Normal jugular venous waveform

- **Normal tracing**: jugular (central) venous pressure waveform is comprised of **five** distinct components (Fig. 2-3):
  - ■ a wave: **a**trial contraction
  - ■ x descent: atrial rela**x**ation (before c wave), downward descent of tricuspid apparatus (after c wave; also called **x' descent**)
  - ■ c wave: **c**losure of tricuspid valve
  - ■ v wave: passi**v**e atrial filling
  - ■ y descent: passive atrial empt**y**ing
- **Respirophasic variation**: in a spontaneously breathing individual, JVP will **decrease** during **inspiration** and **increase** during **exhalation**
- **Measurement**: JVP should be measured at **end-expiration** and **end-diastole** (i.e., just before the c wave)

Chest

■ Venous collaterals (venous obstruction), pectus carinatum or excavatum (connective tissue disorders), barrel chest (emphysema), kyphosis (ankylosing spondylitis)

Abdomen

- Hepatomegaly and ascites (right-sided CHF, constrictive pericarditis), enlarged abdominal aorta (though positive predictive value of enlarged abdominal aorta for diagnosing abdominal aortic aneurysm is only 43% [23]
- **Abdominal bruit**: systolic bruit that lateralizes to one side, suggestive of renovascular disease in hypertensive patients (sensitivity 39%, specificity 99%); diffuse bruit is more likely due to aneurysm [23]

Extremities

- Symmetric edema (CHF), asymmetric edema (venous thrombosis or lymphatic obstruction), Janeway lesion/Osler node (endocarditis), "fingerized" thumb (Holt-Oram syndrome), arachnodactyly (Marfan syndrome)

Vascular examination

- **Arterial bruits**:
  - Caused by turbulent flow through narrowed arteries/arteriovenous fistulas or elevated flow through normal arteries
  - Weak correlation between presence of bruit and presence of significant arterial narrowing
  - **Carotid bruits**: sensitivity of carotid auscultation for a 70–99% stenosis of the common or internal carotid artery is 56%, specificity 91%. Positive predictive value of a carotid bruit is 27%, negative predictive value of the absence of a carotid bruit is 97% [24].
  - **Femoral bruits**: in asymptomatic patients, presence of a femoral bruit increases the likelihood of PAD (LR 4.8, 95% CI 2.4–9.5) [25]

- **Pulses** (Table 2-6):
  - **Pulses to examine**: carotid, radial, brachial, femoral, popliteal, posterior tibial, dorsalis pedis
  - **Normal carotid (aortic) tracing**: consists of three "waves" (Fig. 2-4)

TABLE 2-6

CAROTID ARTERY PULSE

PULSE	ASSOCIATION(S)
Pulsus alternans	**Severe LV dysfunction**, ectopic beats, tamponade
Pulsus paradoxus	**Tamponade**, constrictive pericarditis, restrictive CMP, RV failure (PE, RVMI, tension PTX, cor pulmonale), COPD, asthma, hypovolemia
Pulsus bisferiens	**Aortic regurgitation, HCM**
Dicrotic pulse	**Shock** (hypovolemic, cardiogenic, septic, obstructive)
Pulsus parvus et tardus	**Severe aortic stenosis**
Corrigan pulse	**Severe aortic regurgitation**

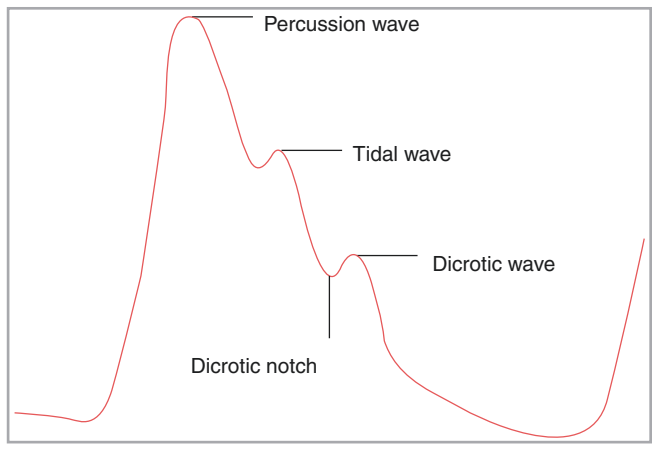


FIGURE 2-4

Normal aortic wave form

- Percussion wave: represents rapid left ventricular ejection into aorta (occurs during **systole**)
- Tidal wave: represents peripheral arterial recoil (occurs during **systole**)
- Dicrotic wave: represents reflected impulse from closure of the aortic valve (occurs during **diastole**)

– **Pulsus alternans**: variation in pulse amplitude between successive beats

- **Causes**: severe **left ventricular systolic dysfunction**, ectopic beats, cardiac tamponade

– **Pulsus paradoxus**: fall in SBP > 12 mmHg with inspiration

- Physiology:
  - During inspiration, decrease in intrathoracic pressure leads to **increased venous return** to the right heart and expansion of the right ventricle → this causes the interventricular septum to **bow into the left ventricle**
  - In normal patients, this leads to only a modest drop in systolic blood pressure on inspiration (<10 mmHg) because the free wall of the left ventricle can expand to accommodate the bulging interventricular septum
  - However, in patients with tamponade, the rigid pericardium prevents the free wall from expanding, leading to an **exaggerated** drop in systolic blood pressure on inspiration (**pulsus paradoxus**)
- Clinical correlation: sensitivity of 98% and specificity of 83% for the diagnosis of pericardial tamponade [8]
- Causes: constrictive pericarditis, restrictive cardiomyopathy, right ventricular failure (e.g., PE, RVMI, tension pneumothorax, cor pulmonale), obstructive lung disease (COPD, asthma), hypovolemia
- Paradoxical pulsus paradoxus: fall in SBP > 12 mmHg with **expiration**; seen in patients on mechanical (positive pressure) ventilation

– **Pulsus bisferiens**: accentuation of both percussion and tidal wave such that two carotid upstrokes are felt, both in **systole** → creates "**spike and dome**" pattern (sharp percussion wave, broad tidal wave) (Fig. 2-5)

- Causes: aortic regurgitation, hypertrophic obstructive cardiomyopathy

– **Dicrotic pulse**: accentuation of dicrotic wave such that two carotid upstrokes are felt, one in **systole** and one in **diastole** (Fig. 2-6)

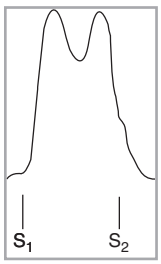


FIGURE 2-5

Aortic tracing representing pulsus bisferiens

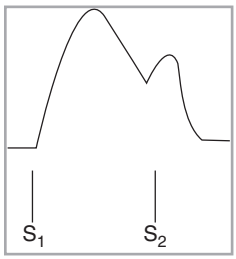
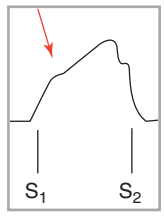


FIGURE 2-6

Aortic tracing representing dicrotic pulse

FIGURE 2-7

Aortic tracing representing pulsus parvus et tardus. The red arrow demonstrates the anacrotic notch



- Causes: **circulatory shock** of various etiologies (hypovolemic, cardiogenic, septic, obstructive) [26]
- Impossible to distinguish from pulsus bisferiens without pressure tracing

– **Pulsus parvus et tardus**: weak (parvus) and delayed (tardus) pulse (Fig. 2-7)

- Cause: **severe aortic stenosis**
- Results in the development of an **anacrotic notch** on the aortic/carotid tracing (notch during aortic/carotid upstroke that precedes the percussion wave) → represents sudden decrease in the rate of acceleration of pressure within the aorta/carotid (the earlier it occurs, the more hemodynamically significant the aortic stenosis)
- Positive likelihood ratio for severe aortic stenosis: 2.8–130 [27]

– **Corrigan pulse**: forceful, bounding pulse with a rapid upstroke and descent → reflects widened pulse pressure

- Cause: **severe aortic regurgitation**
- Mechanism: large stroke volume ejected into the aorta during systole (rapid upstroke) followed by large regurgitant fraction returned to the left ventricle during diastole (rapid descent)
- Similar features can also be detected on examination of the radial pulse (called "**water hammer pulse**") → elicited by raising the patient's arm above the level of the heart while in a reclining position

Cardiac Examination

The cardiac examination is comprised of **three** sections:

Inspection

- **Look for**: visible pulsations, sternotomy scars, implanted devices such as pacemakers or defibrillators, arteriovenous fistulas on extremities

Palpation

- Assess **point of maximal impulse (PMI)**

– Normal: midclavicular line at the fifth intercostal space (LV apex), <2 cm in diameter, quick (NB: may be shifted towards midline in thin, tall people)
– Abnormal: see Table 2-7

Auscultation (Tables 2-8 and 2-9, Fig. 2-8)

VALVULAR DISEASES AND MURMURS

Systolic Murmurs (Tables 2-10 and 2-11)

TABLE 2-7

ABNORMAL POINT OF MAXIMAL IMPULSE

	LEFT 2ND INTER-COSTAL	LEFT PARASTERNAL		APEX		LATERALLY DISPLACED	RIGHT PARA-STERNAL
Quality		Hyper-dynamic	Sustained	Hyper-dynamic	Sustained		
Pathophys.	Dilated PA	↑ RV volume	Significant RVH or space-occupy-ing lesion in R lung			LV dilation or various lung pathology	Massive RV dilation
Cause	■ Severe PH ■ Severe ASD	■ ASD ■ TR	■ PH ■ MS ■ R-sided tension PTX or pleural effusion	■ Severe MR ■ Severe AR ■ PDA ■ VSD ■ High output state (thyroid, storm, anemia)	■ LVOT obstruc-tion ■ HTN ■ Dilated CMP ■ AR with ↓ LVEF	■ Dilated CMP ■ L-sided pulm. fibrosis ■ R-sided tension PTX or pleural effusion	■ Ebstein-anom. ■ Large ASD ■ Severe MS

TABLE 2-8

OVERVIEW OF HEART SOUNDS AND MURMURS

SYSTOLIC		DIASTOLIC		CONTINUOUS
MURMURS	**SOUNDS**	**MURMURS**	**SOUNDS**	**MURMURS**
Early (rare) ■ Small VSD ■ Acute severe MR ■ TR with normal RVSP Mid-systolic ■ AS ■ PS ■ HCM Mid-systolic ejection murmur ■ Benign flow murmur ■ Aortic sclerosis ■ Healthy children and adolescents ■ High flow across valve – Pregnancy – Hyperthyroidism – Anemia – ASD Late systolic ■ MVP Holosystolic ■ VSD ■ MR ■ TR	■ MVP click ■ Ejection click from bicuspid aortic or pulmonic valve ■ Ejection click from aortic or pulmonic root dilation	Early ■ AR ■ PR Mid- to late diastolic ■ MS ■ TS ■ Atrial myxoma	■ Opening snap ■ Pericardial knock ■ Tumor plop	■ PDA ■ Ruptured Sinus of Valsalva aneurysm ■ Arteriovenous fistula ■ Surgical shunts ■ Coarctation of aorta ■ Cervical venous hum ■ Mammary soufflé of pregnancy

TABLE 2-9

HEART SOUNDS

CARDIAC FINDING	CAUSE(S)	PATHOPHYSIOLOGY
S1/S2/Gallops		
Normal S1	Closure of the mitral and tricuspid valves	Best heard over the apex (MV) and left lower sternal border (TV)
Accentuated S1	Mild-mod MS/TS, atrial myxoma	Obstruction to flow across mitral/tricuspid valve (early finding)
	PDA, VSD, ASD, high-output heart failure	Increased flow across mitral/tricuspid flow
	Pre-excitation syndrome + tachycardia	Short PR interval
Decreased S1	Severe MS/TS	Immobile mitral/tricuspid valve (late finding)
	Severe AS, severe acute AR, long PR interval, dilated CMP	Pre-systolic semi-closure of mitral/tricuspid valve
	Severe TR/MR	Lack of apposition of mitral/tricuspid leaflets
	LBBB	Delayed closure of mitral/tricuspid valve due to conduction abnormalities
Wide splitting of S1	TS, ASD, Ebstein's anomaly, RA myxoma	Delayed closure of tricuspid valve due to mechanical causes
	RBBB, LV pacing, PVCs arising from LV	Delayed closure of tricuspid valve due to conduction abnormalities
Paradoxical splitting of S1	Mitral stenosis, LA myxoma	Delayed closure of mitral valve due to mechanical causes
	PVCs arising from RV + underlying LBBB (NB: LBBB alone does **NOT** cause paradoxical splitting of S1)	Delayed closure of mitral valve due to conduction abnormalities
Normal S2	Closure of the aortic and pulmonic valves	Best heard over right (AV) and left (PV) upper sternal border Physiologic splitting of S2: during **expiration**, A2 and P2 are coincident; during **inspiration**, decreased intrathoracic pressure → increased right-sided venous return → delayed P2 closure (i.e., physiologic splitting)
Accentuated A2	Systemic HTN, coarctation of aorta, thoracic aortic aneurysm, TOF	Elevated aortic pressure (HTN, coarctation), anteriorly displaced aorta (TOF)
Accentuated P2	Pulmonary hypertension (PH), ASD	Elevated pulmonary pressure (PH), unknown cause (ASD)
Decreased A2	Severe AS, severe AR	Decreased valve apposition (AR), decreased valve opening (AS)
Decreased P2	Severe PS, severe PR without PH	Decreased valve apposition (PR), decreased valve opening (PS)
Wide splitting of S2	PH, PS, PE	Delayed closure of pulmonic valve due to mechanical causes
	Severe MR	Premature close of aortic valve
	RBBB, WPW with LV bypass tract	Delayed closure of pulmonic valve due to conduction abnormalities
Wide, fixed splitting of S2	Ostium secundum ASD	Shortening of LV ejection time
	Severe RV failure	Inability to vary stroke volume during inspiration leading to loss of respirophasic delay of P2
Paradoxical splitting of S2	Severe AS, HCM, severe myocardial ischemia, severe AR	Delayed closure of aortic valve due to mechanical causes
	LBBB, WPW with RV bypass tract, RV pacing	Delayed closure of aortic valve due to conduction abnormalities

TABLE 2-9

(CONTINUED)

CARDIAC FINDING	CAUSE(S)	PATHOPHYSIOLOGY
S3	Description: low-pitched mid-diastolic gallop best heard over apex/PMI in left lateral decubitus position with bell of stethoscope ("TENN-e-ssee") Physiologic: may be normal in patients <40 years old, high-output states (e.g., pregnancy) Pathologic: severe MR, dilated CMP (predicts reduced EF with sens 32–52%, spec 87–92%) [28]	Rapid passive ventricular filling into a dilated left ventricle
S4	Description: low-pitched late diastolic gallop best heard over apex/PMI in left lateral decubitus position with bell of stethoscope ("ken-TU-cky") Physiologic: age-associated decrease in ventricular compliance Pathologic: LVH, prior MI, severe AS, HCM, severe AR (cor bovinum)	Due to atrial contraction against a stiff left ventricle *Note*: can **never** hear an S4 in atrial fibrillation (no coordinated atrial contraction)
Summation gallop	Loud diastolic gallop that is a fusion of S3 and S4	
Additional sounds		
Aortic ejection click	Description: high-pitched early- to mid-systolic sound best heard at RUSB; occurs **before** carotid upstroke Causes: bicuspid aortic valve, aortic root dilation with normal AV (**absent** in supra- and subvalvular AS)	
Pulmonic ejection click	Description: high-pitched early- to mid-systolic sound best heard at LUSB; occurs **before** carotid upstroke Causes: bicuspid pulmonic valve, pulmonic root dilation with normal PV	*Note*: unlike other right-sided heart sounds, pulmonic ejection click does **not** increase with inspiration
Mid-systolic click	Description: Mid-systolic sound best heard over RUSB or LUSB; occurs **after** carotid upstroke Cause: mitral valve prolapse	
Opening snap	Description: High-pitched diastolic sound best heard at RUSB or LUSB Cause: mitral stenosis	Thickened mitral leaflets become fused at their commissures → during diastole, opening of mitral valve is abruptly halted due to this leaflet fusion → causes opening snap
Pericardial knock	Description: Loud, high-pitched early diastolic sound best heard at RLSB; occurs just before S3 Cause: constrictive pericarditis	Due to abrupt cessation of ventricular expansion during diastole
Tumor plop	Description: Low-pitched diastolic sound Cause: atrial myxoma/tumor, atrial thrombus	Due to prolapse of thrombus/mass through mitral/tricuspid valve upon opening

TABLE 2-9

(CONTINUED)

CARDIAC FINDING	CAUSE(S)	PATHOPHYSIOLOGY
Pericardial friction rub	Description: scratchy, "squeaky leather" sound heard throughout cardiac cycle with three distinct components (one systolic, two diastolic); best heard at left parasternal border with patient leaning forward Cause: pericarditis	Due to friction created by the presence of fluid between the visceral and parietal pericardium Note: can be distinguished from pleural friction rub by asking patient to hold his/her breath (unlike pleural rub, pericardial rub continues to be heard in the absence of respiration)
Distant heart sounds	Causes: Pericardial effusion, pneumothorax, mechanical ventilation, obstructive lung disease, obesity, excess breast tissue	Due to the presence of an extra-cardiac collection (fluid, air, fat tissue) situated between the heart and chest wall

FIGURE 2-8

Pictorial overview of heart sounds and murmurs. *M* mitral, *T* tricuspid, *A* aortic, *P* pulmonary, *E* ejection click, *C* mid-systolic click, *OS* opening snap, *K* pericardial knock

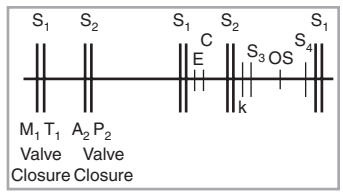


TABLE 2-10

OVERVIEW OF SYSTOLIC MURMURS

MURMUR	DESCRIPTION	ASSOCIATED FINDINGS
Benign systolic murmur ("ejection murmur")	Isolated grade I or II mid-systolic crescendo-decrescendo murmur in the absence of signs/symptoms of underlying heart disease	
Valvular aortic stenosis (AS)	Crescendo-decrescendo, harsh, mid- to late-systolic murmur best heard at the RUSB	■ Radiates to carotids ■ Loud A2 ■ **Severe AS**: late peaking, paradoxically split S2, single/absent S2, pulsus parvus et tardus (*NB*: exam findings correlate well with degree of stenosis) [29] ■ **Gallavardin phenomenon**: loud, harsh, blowing murmur at apex associated with AS (*NB*: frequently misdiagnosed as MR or HCM)
Supravalvular AS	Mid-systolic murmur best heard at RUSB	■ Radiates to R carotid > L carotid
Subvalvular AS	Mid-systolic murmur best heard at LLSB	■ Does not radiate to neck
Hypertrophic cardiomyopathy (HCM)	Crescendo-decrescendo, harsh, mid-systolic murmur best heard at L parasternal border	■ Pulsus bisferiens ■ **Brockenbrough sign**: combination of ↑ LV peak-systolic pressure and ↓ aortic pulse pressure that occurs after PVC (pathophys: pause after PVC → ↑ LV filling time but also ↑ LVOT obstruction → leads to ↑ LV peak-systolic pressure + ↓ aortic pulse pressure)

TABLE 2-10

(CONTINUED)

MURMUR	DESCRIPTION	ASSOCIATED FINDINGS
Pulmonic stenosis (PS)	Crescendo-decrescendo, harsh, mid-systolic murmur best heard at RUSB	■ Radiates to carotids (R > L), posterior lung fields ■ Pulmonic ejection click ■ Widely split S2 ■ **Severe PS**: late peak, evidence of PH (see below)
Mitral regurgitation (MR)	Blowing, holosystolic murmur best heard at apex	■ Radiates anteriorly (posterior leaflet) or to axilla (anterior leaflet) ■ **Acute (severe)**: may best be heard at LLSB, murmur may be absent or occur early in systole ■ **Chronic (severe)**: soft S1, widely split S2, presence of S3, mid-diastolic flow murmur simulating MS (due to ↑ flow across MV); intensity correlates poorly with severity
Tricuspid regurgitation (TR)	Holosystolic murmur best heard at LLSB	■ Radiates to epigastrium ■ Prominent v wave on JVP ■ Hyperdynamic RV impulse (best felt at L parasternal area) ■ RV S3 ■ **Chronic (severe)**: mid-diastolic flow murmur simulating TS (due to ↑ flow across TV) ■ Intensity of murmur increases with inspiration
Pulmonary hypertension (PH)		■ RV heave (L parasternal impulse/lift) ■ Palpable or loud P2 ■ Single S2 ■ TR murmur (*NB*: PR murmur rare)
Mitral valve prolapse (MVP)	Late-systolic, crescendo murmur best heard at apex	■ Mid-systolic click (non-ejection) ■ **Associated with extra-cardiac findings**: muscular dystrophy, Marfan syndrome, Turner syndrome, autosomal dominant polycystic kidney disease, arm span > height span, straight back
Ventricular septal defect	Holosystolic murmur best heard at L parasternal border (location depends on level of VSD)	■ Associated with palpable thrill at left parasternal border ■ The smaller the VSD, the louder (and higher-pitched) the murmur ■ **Eisenmenger syndrome**: absence of holosystolic murmur (due to equalization of RV/LV pressure), mid-systolic murmur (due to dilated pulmonary trunk), signs of PH
Atrial septal defect (ASD)	ASDs do not produce primary murmur	■ Associated with mid-systolic pulmonic ejection murmur ■ Also associated with mid-diastolic mitral flow murmur (due to ↑ flow across MV) ■ Wide, fixed splitting of S2 ■ Hyperdynamic RV impulse (best felt at L parasternal area) ■ If severe, signs of Eisenmenger syndrome will develop (as above)

Diastolic Murmurs (Tables 2-12 and 2-13)

Continuous Murmurs (Table 2-14)

TABLE 2-11

MANEUVERS TO DIFFERENTIATE SYSTOLIC MURMURS

MANEUVER	PATHOPHYSIOLOGY	AS	HCM	MVP	MR
Inspiration[a]	↑ R-sided venous return	↓	↓	↓	↓
Expiration[a]	↓ R-sided venous return	↑	↑	↑	↑
Handgrip	↑ afterload	↓	↓	↓	↑
Amyl nitrite	↓ afterload	↑	↑	↑	↓
Squatting, passive leg raise	↑ preload	↑	↓	↓[b]	↑
Standing, Valsalva maneuver	↓ preload	↓	↑	↑[c]	↓
Post-PVC beat	↑ contractility + ↑ preload	↑	↑	↔	↔

[a]**Note**: **right-sided murmurs** increase with **inspiration** (Carvallo's sign); **left-sided murmurs** increase with **expiration**
[b]Mid-systolic ejection click moves **further** from S1 (due to ↑ LV volume → ↓ prolapse)
[c]Mid-systolic ejection click moves **closer** to S1 (due to ↓ LV volume → ↑ prolapse)

TABLE 2-12

OVERVIEW OF DIASTOLIC MURMURS

MURMUR	DESCRIPTION	ASSOCIATED FINDINGS
Aortic regurgitation (AR)	High-pitched, blowing, early diastolic decrescendo murmur best heard at: ■ LUSB: primary AR ■ RUSB: secondary AR (due to root dilation)	■ Best auscultatory position: leaning forward at end-expiration ■ Pulsus bisferiens ■ **Diastolic whoop**: late diastolic extra sound due to flail everted aortic cusp ■ **Acute (severe)**: early and short diastolic murmur (may be absent), decreased S1 (due to early closure of MV), decreased A2, accentuated P2 (due to PH), mid-systolic ejection click (due to acute aortic dissection caused by large stroke volume), normal pulse pressure ■ **Chronic (severe)**: decreased S1, decreased A2, S3 with displaced PMI, paradoxical splitting of S2 (due to delayed AV closure in the setting of ↑ stroke volume), mid-systolic flow murmur simulating AS (due to ↑ flow across AV), **Austin Flint murmur** (low-pitched, mid-diastolic murmur with pre-systolic accentuation best heard at the apex; responds to maneuvers similarly to main AR murmur), peripheral signs of **widened pulse pressure** (below): – Quincke's pulse: capillary pulsation in fingernails – de Musett's head bob: head bob with each heart beat – Corrigan (water hammer) pulse: forceful, bounding pulse with sudden collapse – Hill's sign: popliteal SBP > 20 mmHg ↑ than brachial SBP – Duroziez's sign: systolic + diastolic bruit upon partial compression of femoral artery – Systolic pulsations of: liver, spleen, uvula, retina, cervix, nasal mucosa
Pulmonic regurgitation (PR)	Blowing, early diastolic decrescendo murmur best heard at LUSB	■ Mid-systolic flow murmur simulating PS (due to ↑ flow across PV) ■ **Primary (– PH)**: low-pitched, soft murmur ■ **Secondary (+ PH)**: high-pitched, loud murmur, evidence of PH (see Table 2-8), **Graham Steell murmur** (accentuated P2 followed by typical PR murmur)

TABLE 2-12

(CONTINUED)

MURMUR	DESCRIPTION	ASSOCIATED FINDINGS
Mitral Stenosis (MS)	Rumbling, late diastolic murmur best heard at apex	■ Best auscultatory position: left lateral decubitus position using bell of stethoscope ■ Increased S1 (mild-mod) ■ Opening snap (OS) ■ Pre-systolic accentuation (increase in murmur intensity immediately preceding S1) ■ **A2-OS interval**: inversely correlates with MS severity and duration of diastolic murmur (more severe MS → increased LA pressure → decreased LA-LV pressure gradient → earlier onset of OS and subsequent murmur → longer duration of murmur) ■ **Severe MS**: decreased S1 and OS, short A2-OS interval (longer duration of murmur), evidence of PH/RVH, mitral facies (pinkish-purple patches on cheeks reflecting ↓ SBP and subsequent vasoconstriction)
Tricuspid Stenosis (TS)	Rumbling, late diastolic murmur best heard at LLSB	■ Opening snap ■ Prominent a wave, blunted y descent on JVP ■ Pre-systolic hepatic pulsation ■ Often associated with MS
Atrial Myxoma	Mid- to late diastolic murmur due to obstruction of valve by myxoma (MV > TV)	■ Tumor plop ■ Accentuated or split S1 ■ Similar in character to MS murmur, often difficult to distinguish

TABLE 2-13

MANEUVERS TO DIFFERENTIATE DIASTOLIC MURMURS

MANEUVER	PATHOPHYSIOLOGY	AR	MS
Inspiration	↑ R-sided venous return	↓	↓
Expiration	↓ R-sided venous return	↑	↑
Handgrip	↑ afterload	↑	↑[a]
Amyl nitrite	↓ afterload	↓	↑[a]
Squatting, passive leg raising	↑ preload	↑	↑
Standing, Valsalva maneuver	↓ preload	↓	↓
Post-PVC beat	↑ contractility + ↑ preload	↑	↑

[a]**Mitral stenosis**: unique in that its murmur increases with both handgrip (due to compensatory ↑ in heart rate) *and* amyl nitrate (due to ↑ forward flow and cardiac output)

TABLE 2-14

OVERVIEW OF CONTINUOUS MURMURS

MECHANISM	EXAMPLES
High-to-low pressure shunts	**PDA** (machinery murmur with maximal intensity at S2), aortopulmonary window, arteriovenous fistula, ruptured sinus of Valsalva aneurysm, surgical cardiac shunts (e.g., Blalock, Waterston, Potts)
Aortic or pulmonary artery constriction (due to flow through collateral vessels)	**Coarctation of aorta** (best heard over posterior spine), pulmonary artery stenosis
Rapid blood flow (benign)	**Cervical venous hum** (best heard at supraventricular fossa, disappears when patient is supine or when internal jugular vein is compressed), **mammary soufflé** (heard over breast in pregnant women)

QUICK REVIEW

Questions and Answers:

1. A healthy 24-year-old man presents to cardiology clinic for a pre-sports participation physical examination. He was born in Nigeria but moved to the United States when he was 11 years old. He denies a history of medical problems, although he does recall having several episodes of febrile pharyngitis as a child. He is asymptomatic and denies chest pain, palpitations, shortness of breath, fatigue, or weight loss. He is 6 ft 4 in. tall and weighs 181 pounds (BMI 22). On physical examination, the patient is noted to have a III/VI systolic murmur best heard at the right parasternal border, a faint I/IV diastolic murmur best heard at the left upper sternal border, and a mid-systolic extra sound that is heard before the onset of the carotid upstroke is palpated. The murmur decreases in quality with isometric handgrip exercises.

   Which of the following interventions is the patient most likely to need?

   a) Placement of implantable cardioverter defibrillator (ICD)
   b) Yearly screening for thoracic aortic aneurysm
   c) Surgical resection of left atrial tumor
   d) Mitral balloon valvuloplasty

   Answer: b

   The patient's physical exam characteristics are consistent with a **bicuspid aortic valve**. Bicuspid aortic valve is the most common congenital valvular condition, affecting approximately 1% of the population. It may be seen in isolation or associated with other cardiovascular conditions, including coarctation of the aorta, supravalvular and subvalvular aortic stenosis, ventricular septal defect, patent ductus arteriosus, and sinus of Valsalva aneurysm. It also may be associated with congenital conditions such as Turner syndrome, Marfan syndrome, and Ehlers-Danlos syndrome. Physical exam may reveal a harsh, crescendo-decrescendo systolic murmur at the right upper sternal border (aortic stenosis), a blowing diastolic murmur at the left upper sternal border (aortic regurgitation), or less commonly both. Bicuspid aortic valves are also associated with mid-systolic aortic ejection clicks that are heard before the carotid upstroke is palpated. In patients with aortic stenosis, isometric handgrip exercise tends to decrease the intensity of the murmur by increasing systemic afterload, thereby decreasing the gradient across the stenotic aortic valve.

   Given the association between bicuspid aortic valves and thoracic aortic aneurysms, patients with bicuspid aortic valves should undergo routine surveillance of the aortic root and ascending aorta via computed tomography or echocardiography (**choice B**).

   Placement of an implantable cardioverter defibrillator may be indicated in patients with hypertrophic obstructive cardiomyopathy (**choice A**). This condition is not associated with a mid-systolic ejection click or a diastolic murmur.

   Atrial myxoma is associated with a diastolic murmur and a tumor plop, which is a diastolic extra heart sound that may be associated with an accented and/or split S1 (**choice C**). It is not associated with a systolic murmur.

   Mitral stenosis may be seen in young adults with a history of acute rheumatic fever. Mitral stenosis is classically associated with a rumbling diastolic murmur and an opening snap, which is a diastolic extra heart sound that results from the abnormal fusion of the mitral leaflet commissures. Selected patients with mitral stenosis may be candidates for balloon valvuloplasty (**choice D**). Mitral stenosis is not associated with a harsh systolic murmur.

2. A 65-year-old woman comes to clinic due to several months of bilateral leg pain, particularly when she walks. She states that after walking two blocks, she develops numbness in both calves and upper thighs (right leg worse than left leg) that progresses to weakness with continued walking. The patient's symptoms worsen when she walks downhill, and her symptoms subside with rest. The patient's medical problems include hypertension, hyperlipidemia, 15-pack-year smoking history, gastrointestinal reflux disease, and degenerative joint disease.

   On examination, the patient's blood pressure is 154/88 and her pulse is 74 beats per minute. A bruit is heard over her left carotid artery. There are no abdominal or femoral bruits. Her femoral, popliteal, posterior tibial, and dorsalis pedis pulses are normal and symmetric. Straight leg raise test is negative. Strength, sensation to light touch, and deep tendon reflexes are normal in both legs.

   Which of the following would best establish the correct diagnosis?

   a) Ankle-brachial index
   b) Pulse volume recording
   c) MRI of lumbar spine
   d) Nerve conduction studies

   Answer: c

   The patient's clinical presentation is most consistent with **lumbar spinal stenosis** (**choice B**). Lumbar spinal stenosis commonly occurs in elderly individuals as a result of cervical spondylosis (degenerative arthritis). This results in spinal canal narrowing and subsequent spinal cord impingement. Patients typically present with bilateral leg pain (often asymmetric and involving the entire leg rather than just the calf), numbness, parasthesias, and/or weakness. Pain is classically exacerbated by walking ("pseudoclaudication"), standing, and extension of the back and is often confused with vascular claudication. Diagnosis is made via MRI of the lumbar spine.

   Pseudoclaudication can be differentiated from vascular claudication (**choice A**) via a careful history and physical examination. Patients with pseudoclaudication report symptom relief with flexion of the back (i.e., leaning over a shopping cart) and symptom exacerbation with downhill walking. In contrast, patients with vascular claudication report symptom exacerbation with uphill walking; back flexion or extension does not typically relieve or exacerbate pain. On physical examination, patients with pseudoclaudication will have normal, symmetric pulses and non-atrophic skin. Patients with claudication typically demonstrate pulse deficits and brittle, shiny, and hairless skin over the affected limb.

   Bone scan may be useful to diagnose metastatic spinal lesions (**choice C**), but the lack of point tenderness over the spine or signs/symptoms of cauda equina syndrome argue against this condition.

   Nerve conductions studies are used to diagnose peripheral neuropathy (**choice D**), but the lack of radicular or sensory symptoms argues against this condition.

3. A 37-year-old female with a history of generalized anxiety disorder presents for routine physical examination. She experiences intermittent palpitations but is otherwise well. Cardiac examination is notable for a mid-systolic click heard at the cardiac apex without a detectable murmur. Upon standing from a squatting position, the click is appreciated earlier in systole.

Which of the following is the most likely diagnosis?

a) Atrial myxoma
b) Mitral valve prolapse
c) Constrictive pericarditis
d) Mitral valve stenosis
e) Normal mitral valve

Answer: b

The patient's physical examination findings are consistent with **mitral valve prolapse (choice B)**. Upon standing, venous return decreases, causing the mitral valve to prolapse sooner due to a decrease in left ventricular volume. On exam, this is reflected by the occurrence of the mid-systolic click earlier in systole (i.e., it is heard closer to S1). Conversely, squatting causes an increase in venous return and left ventricular volume, delaying the prolapse of the mitral valve and resulting in the occurrence of the mid-systolic click later in systole (i.e., it is heard further from S1).

Atrial myxoma **(choice A)** is associated with a tumor plop, which is a soft diastolic extra heart sound best heard at the cardiac apex that may be associated with an accentuated and/or split S1. Constrictive pericarditis **(choice C)** is associated with a pericardial knock, which is a loud diastolic extra heart sound best heard at the right lower sternal border. Neither a tumor plop nor a pericardial knock is affected by positional maneuvers.

Mitral valve stenosis **(choice D)** is associated with a diastolic opening snap followed by a rumbling, low pitched diastolic murmur best heard at the cardiac apex. The opening snap and diastolic murmur of mitral stenosis are not affected by positional maneuvers.

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CHAPTER 3

MICHAEL T. OSBORNE, VINIT BALIYAN, AND BRIAN B. GHOSHHAJRA

Cardiac Noninvasive Imaging: Chest Radiography, Cardiovascular Magnetic Resonance and Computed Tomography of the Heart

CHAPTER OUTLINE

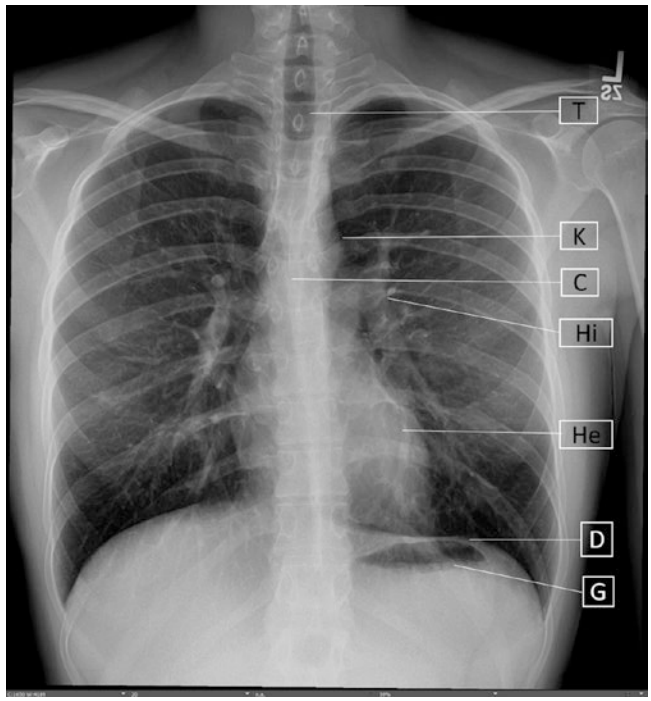
CHEST RADIOGRAPHY

Advantages

Quick, portable, minimal radiation (0.02 millisieverts [mSv]), useful for serial follow-up

FIGURE 3-1

Normal frontal CXR demonstrating normal morphologic anatomy with normal thoracic and abdominal situs. C - Carina, D - diaphragm, G - gastric bubble, He - Heart, Hi - pulmonary hilum, K - Aortic knuckle, T - trachea



Normal Chest X-Ray (CXR) Findings (Fig. 3-1)

Heart

- Normal cardiothoracic ratio of the heart width to the chest width is <50% on postero-anterior (PA) projection, in adults.

Diaphragm

- Normal chest expansion on CXR: 6 ± 1 anterior ribs or 9 ± 1 posterior ribs, right hemi-diaphragm higher than the left by up to 3 cm in 95% of cases

Hila

- Left hilum usually higher by approximately 1 cm than the right hilum, equal density

Abnormal CXR Findings

Dextroposition

- In situs solitus, the position of the heart is on the right side secondary to a non-cardiac abnormality (e.g., scoliosis, pneumonectomy, pulmonary agenesis, right pneumothorax, chronic volume loss or diaphragmatic hernia)

Dextrocardia with situs inversus

- Heart on the right side with inverted abdominal viscera and lung morphology (Fig. 3-2)
- Thoracic situs is determined by the anatomy of the trachea and lungs, not the position of aortic arch or cardiac apex.

Dextroversion

- Counter-clockwise rotation of a normally developed heart in the right hemithorax. On CXR, the apex is not evident as it lies behind the sternum, the left heart border is formed by the left atrium, the right border is formed by the right ventricle (RV) and the right atrium is in a posterior position. The aortic knob is in the normal left-sided position.

"Boot-shaped" heart

- Hallmark of Tetralogy of Fallot, due to right ventricular hypertrophy. The apical curvature of the left heart border is elevated "coeur en sabot" (Fig. 3-3).

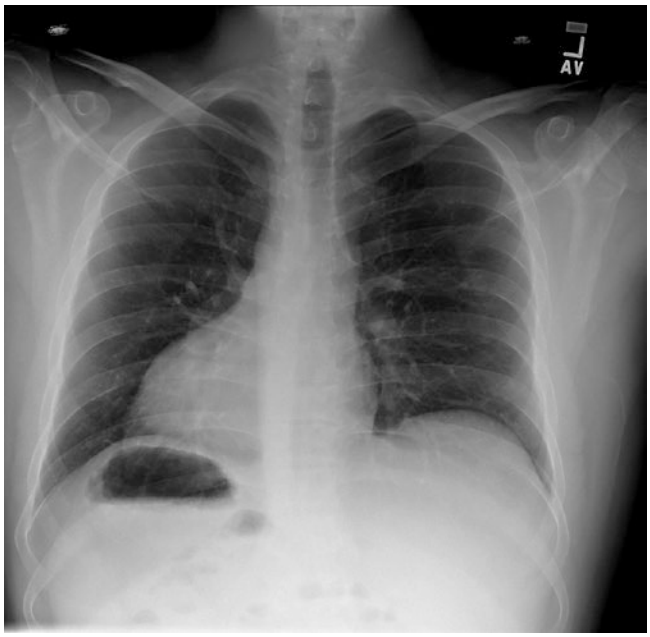


FIGURE 3-2

Dextrocardia with situs inversus. Frontal CXR demonstrating both the cardiac apical silhouette and gastric air bubble are on the right side. Note the "L" marker on the upper right hand corner signifying left

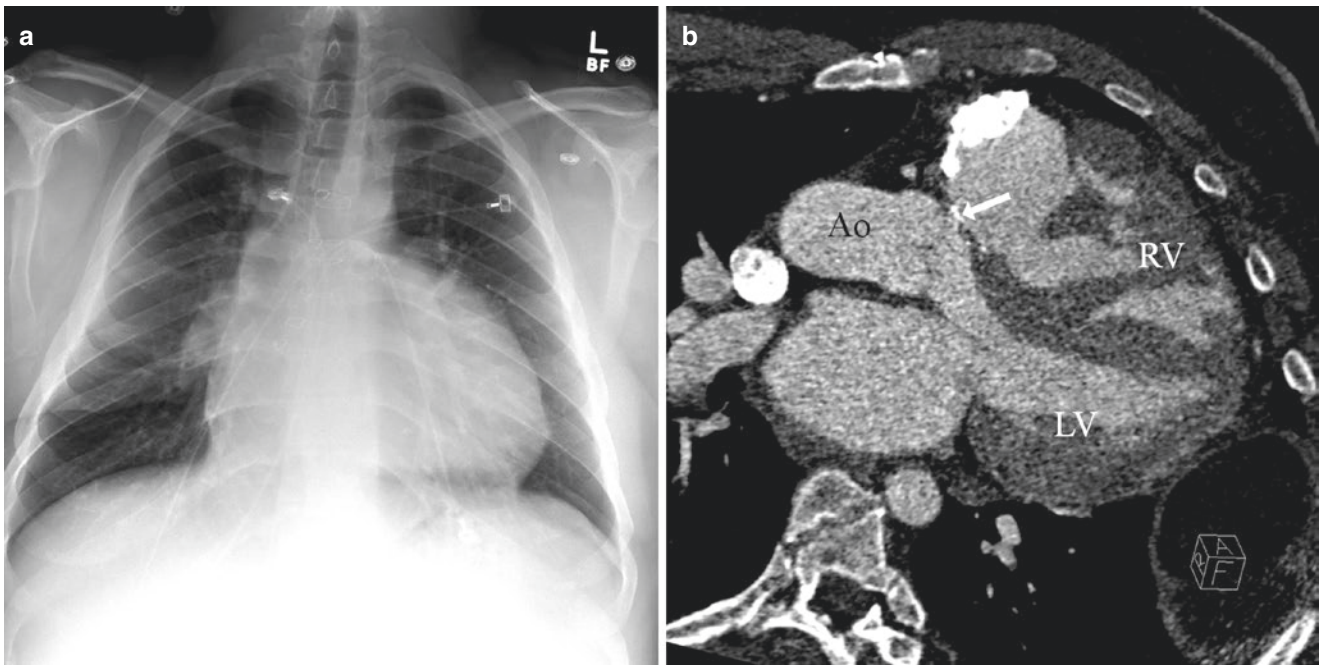


FIGURE 3-3

Tetralogy of Fallot. (**a**) CXR showing elevation of the apical curvature of the left heart border known as "coeur en sabot". (**b**) Cardiac CT showing an overriding aorta (Ao), ventricular septal defect patch (arrow), and right ventricular (RV) hypertrophy. The pulmonary stenosis is not shown on this CT slice. LV: left ventricle

Mediastinal enlargement

- Technical factors causing width of mediastinum to appear exaggerated: patient positioning, antero-posterior (AP) projection or incomplete inspiration
- Pathological causes: aortic aneurysm/dissection, lymphadenopathy, thyroid, thymus, tumor, hemorrhage

Enlarged cardiac silhouette

- Pericardial effusion, left ventricular (LV) dilatation, LV aneurysm

Unequal hilar densities
- Rotated film, lymph nodes, tumor

Hilar enlargement
- Pulmonary hypertension, lymphadenopathy (tuberculosis, sarcoid, lymphoma)

Elevated hemidiaphragm
- Loss of lung volume, phrenic nerve palsy (e.g., post coronary artery bypass graft surgery), subpulmonic effusion, subphrenic abscess, diaphragmatic rupture (e.g., traumatic), hepatomegaly

Increased translucency in lung fields
- Pneumothorax (absent vascular markings with visible lung border), pulmonary hypertension, pulmonary emboli, hyperinflation and bullous changes in chronic obstructive pulmonary disease

Cardiopulmonary Abnormalities/Diseases on CXR

Heart Failure
- Cardiomegaly
- Kerley A lines: long (2–6 cm), unbranching lines seen coursing diagonally towards the hila caused by distension of anastomotic channels between peripheral and central lymphatics of the lungs. Kerley A lines are not seen without Kerley B or C lines
- Kerley B lines: thickened interlobular septa visible as short linear opacities (1–2 cm) in the subpleural regions indicative of interstitial pulmonary edema
- Kerley C lines: seen as fine reticular opacities which may represent anastomotic lymphatics or superimposition of many Kerley B lines. Kerley C lines do not reach the pleura and do not course radially away from the hila
- Peribronchial cuffing due to edema of the bronchial walls and peribronchial connective tissues
- Poor distinction of lower lobe pulmonary vessels
- Greater caliber of upper lobe vessels to lower lung zones
- Pulmonary hila become enlarged and hazy
- Bilateral patchy alveolar opacities (bat's wing appearance)
  - Pleural effusions
  - Chronic left atrial (LA) hypertension results in pulmonary hypertensive changes, RV dilatation.
- LA enlargement
  - Straightening of LA appendage segment between level of the main pulmonary artery and LV on the left heart border, double density to the right of the spine on PA CXR with increasing LA enlargement, splaying of carina >90°

Pulmonary embolism
- Oligemia
- "Westermark sign": a dilatation of the pulmonary vessels proximal to an embolism along with collapse of distal vessels, sometimes with a sharp cutoff
- Hampton hump: a triangular or rounded pleural-based infiltrate with the apex pointed toward the hilum, suggestive of pulmonary infarction

Pulmonary hypertension
- Gradual taper of caliber between dilated central and hilar pulmonary arteries and smaller peripheral vessels (Fig. 3-4), if secondary to left–to-right shunting, the peripheral shunt vessels branch and extend towards the lung periphery

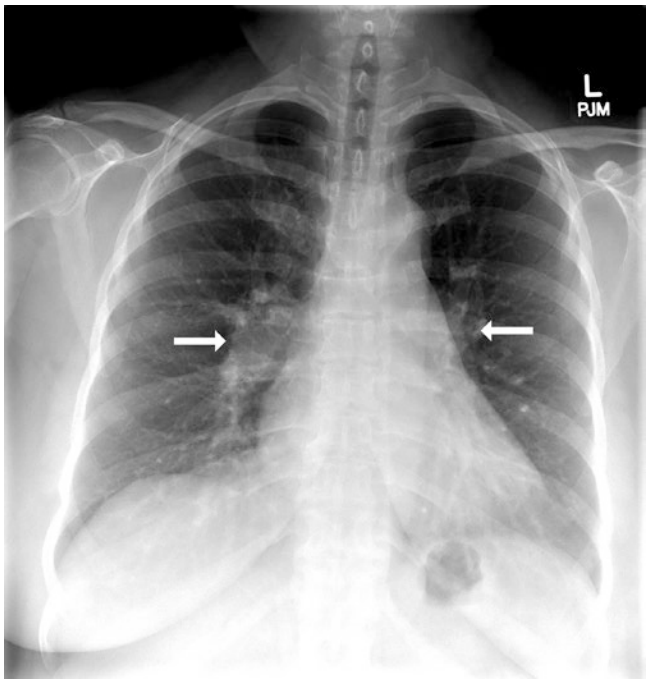


FIGURE 3-4

Pulmonary hypertension. CXR showing prominence of the main pulmonary artery and dilated left and right pulmonary arteries (arrows) associated with pruning of the peripheral pulmonary vasculature

Reduced pulmonary blood flow

- Small caliber central and hilar pulmonary arterial branches, reduced pulmonary vascular markings, seen in Tetralogy of Fallot, pulmonary atresia with ventricular septal defect, Ebstein's anomaly, tricuspid atresia

Right ventricular hypertrophy

- The RV is a midline and anterior structure and thus does not form a cardiac border in the PA projection; however, in RV hypertrophy the apex may be elevated from the diaphragm and the left lower cardiac contour may become more rounded.

Scimitar syndrome

- Partial or total anomalous pulmonary venous return of the right lung veins to the inferior vena cava just above or below the diaphragm, frequently associated with right lung and right pulmonary artery hypoplasia
- PA CXR: decrease in the size of the right thorax, shift of mediastinal structures and heart to the right, presence of anomalous vein "scimitar" as a vertical structure coursing towards the right cardiophrenic angle closely in parallel with the right atrial border

Pericardial Abnormalities

Pericardial Effusion

- An abrupt asymmetrical change in the dimension of the cardiac silhouette without a change in the cardiac chamber size, larger effusions result in the appearance of a 'globular shaped heart, 'fat pad' sign on lateral CXR is positive when an anterior pericardial stripe (separation by pericardial fluid between the pericardial fat posteriorly from the mediastinal fat anteriorly) is thicker than 2 cm
- Echocardiography is most commonly used to confirm the diagnosis.

Pericardial calcification

- Irregular calcification along the heart border, coexisting cardiac enlargement if large pericardial effusion (Fig. 3-5)

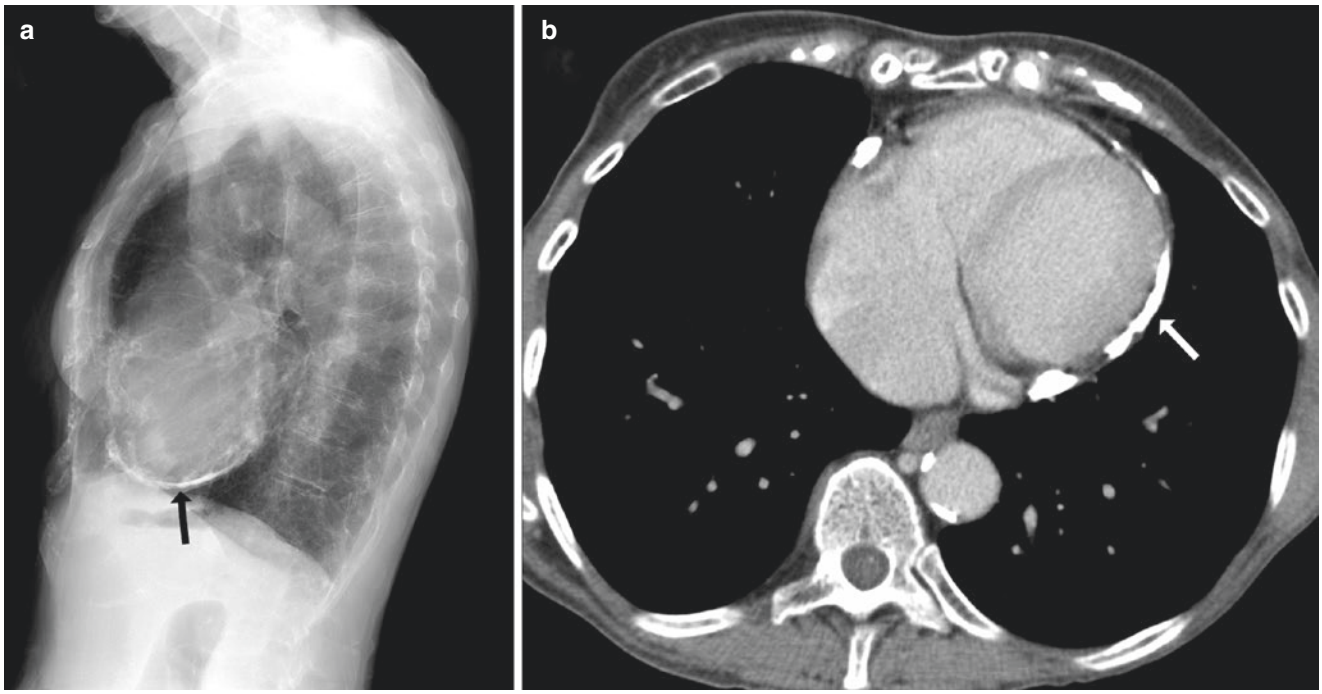


FIGURE 3-5

Pericardial calcification. (**a**) CXR and (**b**) CT image demonstrating calcification along the inferior cardiac border (arrow)

Pericardial cyst

- Well demarcated, rounded mass more commonly near the right cardiophrenic border than the left cardiophrenic border, can have a pointed upper border, pericardial diverticulae changes contours and size during deep inspiration

Congenital absence of the pericardium

- "Snoopy sign" with displacement of the LV and pulmonary artery towards the left side

Abnormalities of the Aorta

Calcification usually signifies degenerative intimal change (e.g., from atherosclerosis).

Coarctation

- "3" sign due to diminution of aortic arch segment with a concave notch in the proximal descending aorta and interruption of the descending aorta shadow distal to the coarctation, rib notching evident if retrograde collateral flow to the post-coarctation aorta by dilated intercostal arteries (Fig. 3-6)

Thoracic aorta dilatation

- Increased curvature of the mid right heart border on PA projection or anterior aortic border on lateral projection suggest ascending aortic enlargement

Aortic dissection

- Prominent aortic arch from hypertension, atherosclerosis, connective tissue disorders, vasculitis, bicuspid aortic valve, blunt chest trauma or iatrogenic causes
- Dissection flap is usually not directly visualized on radiographs, but associated aortic dilation can be seen. Abnormal if diameter >4 cm, focal pathological dilatation especially with widening of the arch beyond the origin of the left subclavian artery (Fig. 3-7)
- Other CXR findings may include obliteration of the aortic knob, tracheal deviation, depression of the left main stem bronchus.
- Pleural effusions, usually left sided, are associated with descending aortic dissection.

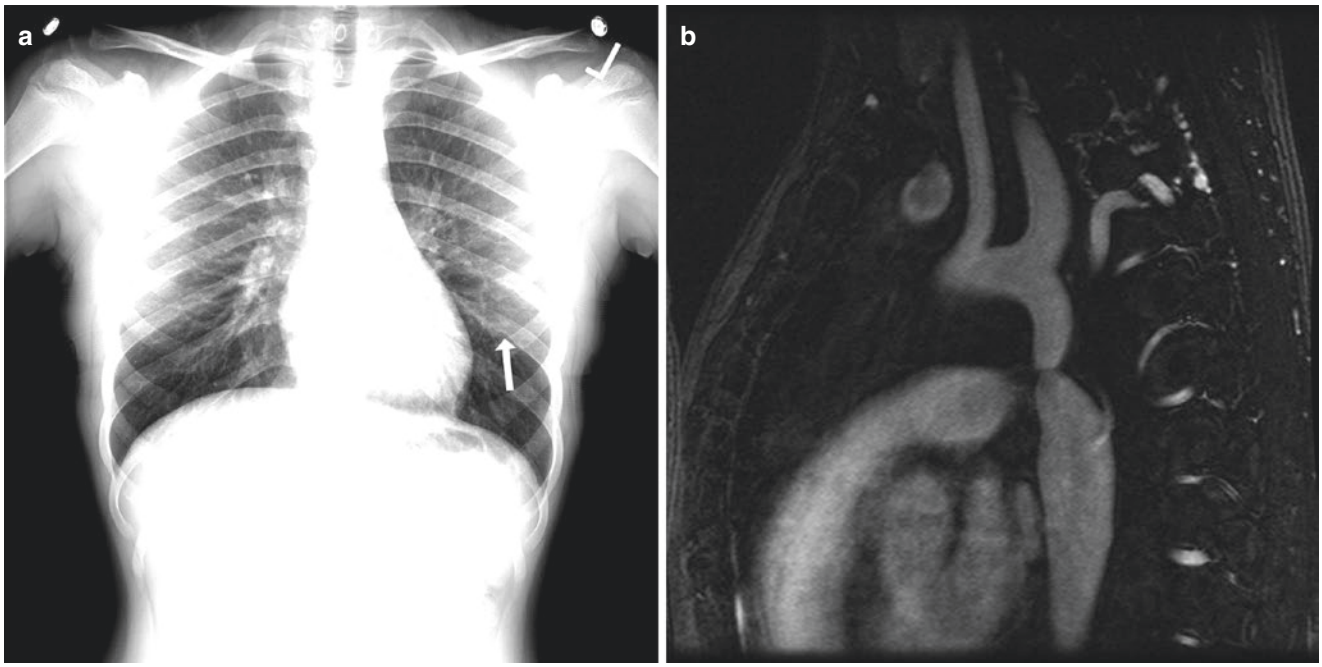


FIGURE 3-6

Aortic coarctation. (**a**) CXR showing left sided rib notching (arrow) due to retrograde collateral flow to the post-coarctation aorta by dilated intercostal arteries. (**b**) Cardiac Magnetic Resonance angiography demonstrating the aortic coarctation in the same patient

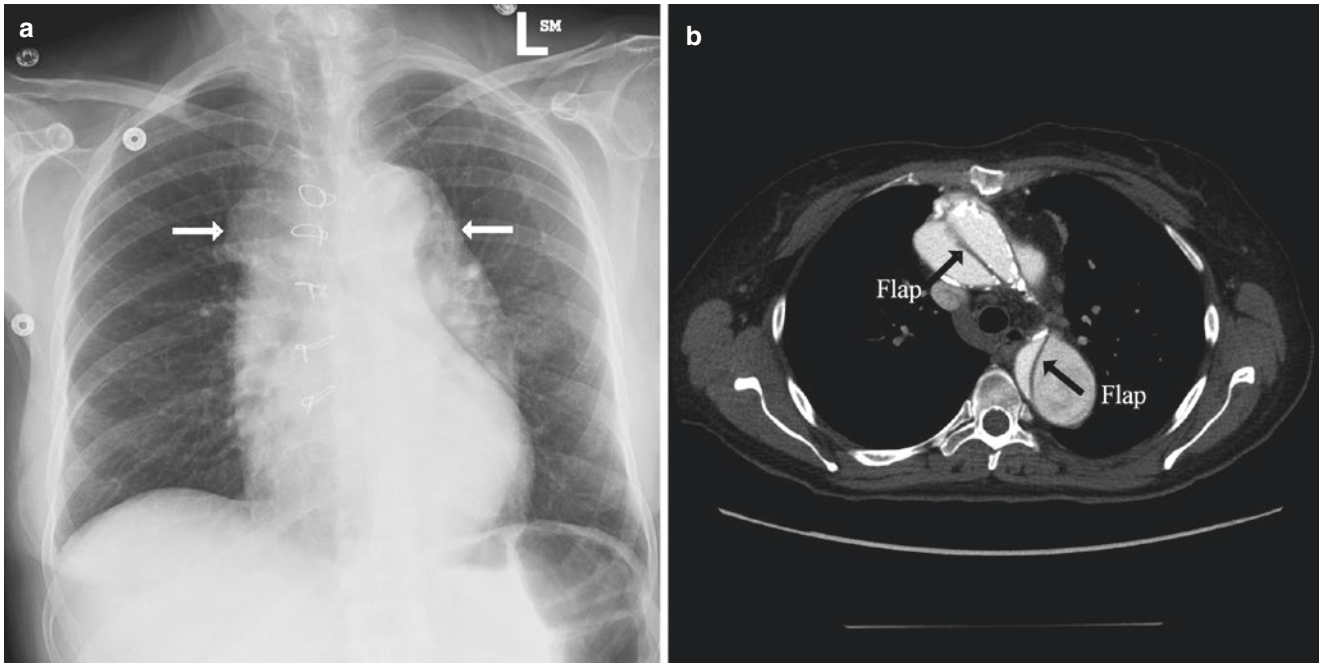


FIGURE 3-7

Aortic dissection. (**a**) CXR demonstrating a widened mediastinum (> 6–8 cm. 4 cm is for aorta, white arrows) in a patient with aortic dissection after blunt chest trauma. (**b**) Cardiac CT confirms a DeBakey Type 1 aortic dissection where the intimal tear/dissection flap (black arrows) originates in the ascending aorta and propagates to the aortic arch and descending aorta

Right-sided aortic arch

- The descending aorta typically runs parallel to the spine in continuity to the aortic arch on the left side on PA CXR, except in cases of a right sided aortic arch.

Identification of Valvular Prostheses on CXR (Fig. 3-8)

- Apart from homografts, all valves are radio-opaque.
- Caged valves and heterografts: direction of flow is from the base ring to the struts
- Disc valves: the direction of flow is appreciated if the disc is seen in an open position

Aortic valve

- The opening of the valve ring is directed more vertically, facing obliquely and to the right. The aortic valve is usually higher, smaller and more anterior to the mitral valve on lateral CXR, and the perceived direction of blood flow is towards the ascending aorta.

Mitral valve

- The mitral valve is situated lower and more to the left than the aortic valve with a perceived direction of flow towards the apex.

Tricuspid valve

- Aligned in a medial-lateral direction, to the right of mitral valve and below the aortic valve

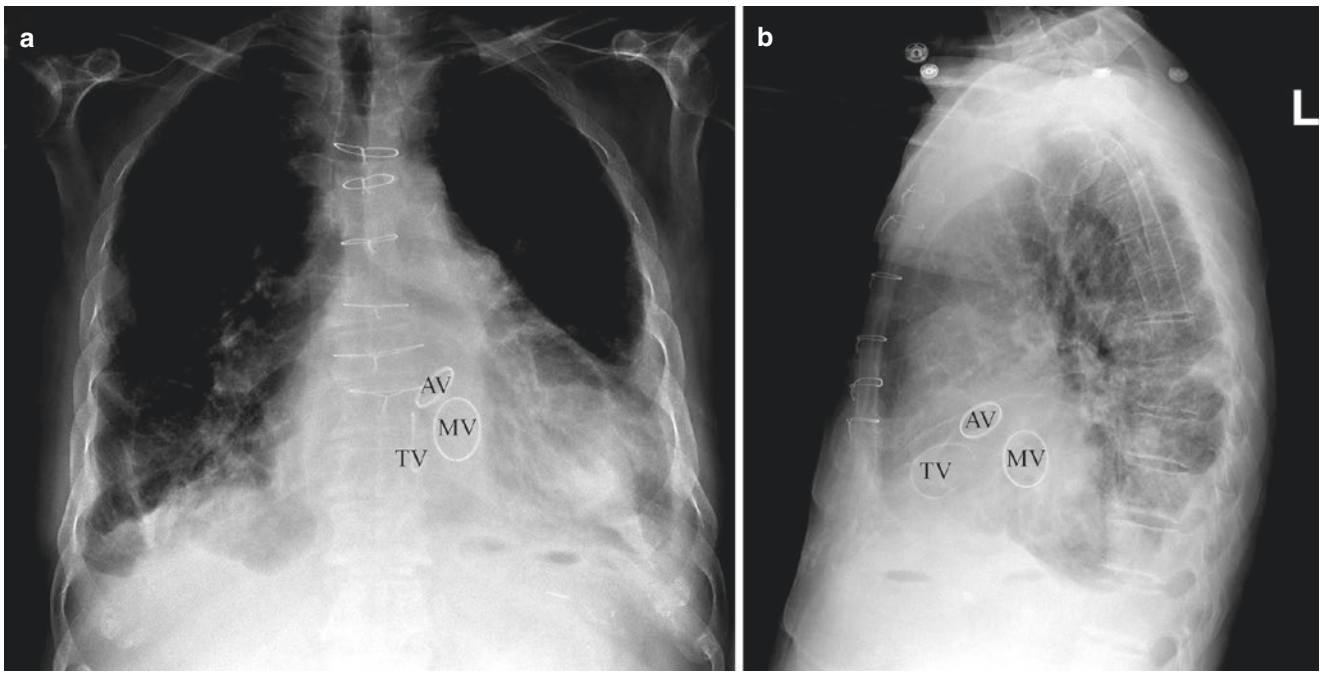


FIGURE 3-8

(**a**) Frontal and (**b**) lateral CXR demonstrating the anatomic relationship of a patient with prosthetic aortic (AV) and mitral valve (MV) replacements and tricuspid valve (TV) annuloplasty ring. The AV is situated higher and is smaller and more anterior to the MV on the lateral CXR. The TV annuloplasty ring is aligned medial-laterally and is positioned to the right of and below the AV

CARDIAC COMPUTED TOMOGRAPHY (CT)

All current multi-detector CT scanners (64-, 256- and 320-slice scanners) have similar temporal and spatial resolutions (100–200 ms temporal, 0.4 mm spatial), however the increased detector rows allow more coverage of the heart in each heartbeat, or even complete coverage of the heart in a single beat. Dual source CT scanners consist of two X-ray tube sources leading to improved temporal resolution to as low as 66 ms.

Advantages and Disadvantages of Cardiac CT (Table 3-1)

CT Scan Acquisition Modes (Table 3-2)

Appropriate CT Indications

2010 Appropriate use criteria for cardiac computed tomography [1].

TABLE 3-1

ADVANTAGES AND DISADVANTAGES OF CARDIAC CT

ADVANTAGES OF CT	DISADVANTAGES OF CT
Rapid scan acquisition	Ionizing radiation
Excellent isotropic spatial resolution (XYZ plane)	Iodinated contrast complications e.g. extravasations, allergy, nephropathy
Compatible with metal devices	Metal devices causes beam hardening artifacts
Contrast able to be hemodialyzed	Diagnostic accuracy may be reduced by heart rate >70 beats per minute, irregular rhythm, severe coronary calcification, inability to sustain breath hold for at least 5–10 s
Allows arterial, venous and functional cardiac assessment	Less accurate assessment of coronary stent with diameter <3 mm

TABLE 3-2

CT SCAN ACQUISITION MODES

CT SCAN MODE	SCAN TECHNIQUE	ADVANTAGES	DISADVANTAGES
Non-contrast enhanced scans			
Calcium score	Non-contrast scan where calcium (>130 Hounsfield Units) is detected	■ Non-contrast ■ Prognostic information	■ Does not assess stenosis severity or other plaque morphology (non-calcified or mixed plaques)
Contrast enhanced scans			
Non-ECG gated	Scan acquisition without ECG synchronization	■ More readily available scanners and technologists ■ Adequate for most aorta and pulmonary assessment	■ Motion artifact ■ Not adequate for coronary or aortic root evaluation
Prospective ECG-triggered	Images acquired at a pre-defined set duration after the QRS complex	■ Radiation reduction as X-ray tube on only at pre-determined phase of the cardiac cycle	■ Limited functional assessment ■ Potential for misregistration or slab artifacts if ectopy or heart rate variability
Retrospective ECG-gated	X-ray current continuously delivered throughout the cardiac cycle	■ Functional assessment; over the enitre duration of cardiac cycle ■ Allows reconstruction at multiple points in the cardiac cycle	■ Higher radiation

Indications for Non-contrast Coronary Calcium Score (CCS)

Risk assessment in asymptomatic patients without known coronary artery disease (CAD):

- At intermediate risk of CAD (correlates with 10-year absolute coronary heart disease (CHD) risk between 10% and 20%)
- At low risk of CAD (correlates with 10-year absolute CHD risk <10%) with a family history of premature CAD
  - Patients with an Agatston score of >400 have a 10-fold increased risk of cardiac events compared to a score of 0 [2].
  - The absence of calcium does not imply no significant coronary stenosis as 8–10% of stenoses can be caused by non-calcified plaque.

Indications for CT Angiography (CTA)

Detection of CAD in symptomatic patients without known CAD who present with:

- **Non-acute symptoms** (stable chest pain) possibly representing an ischemic equivalent with
  - intermediate pretest probability of CAD, or
  - low pretest probability of CAD with uninterpretable electrocardiogram (ECG) or unable to exercise
- **Acute symptoms** with suspicion of acute coronary syndrome, low to intermediate pretest probability of CAD without high risk ECG changes or elevated cardiac biomarkers (Fig. 3-9)

Detection of CAD in other clinical scenarios

- Newly diagnosed clinical heart failure with no prior CAD and reduced LV ejection fraction (low to intermediate pretest probability of CAD)
- Pre-operative coronary assessment prior to non-coronary cardiac surgery (intermediate pretest probability of CAD)

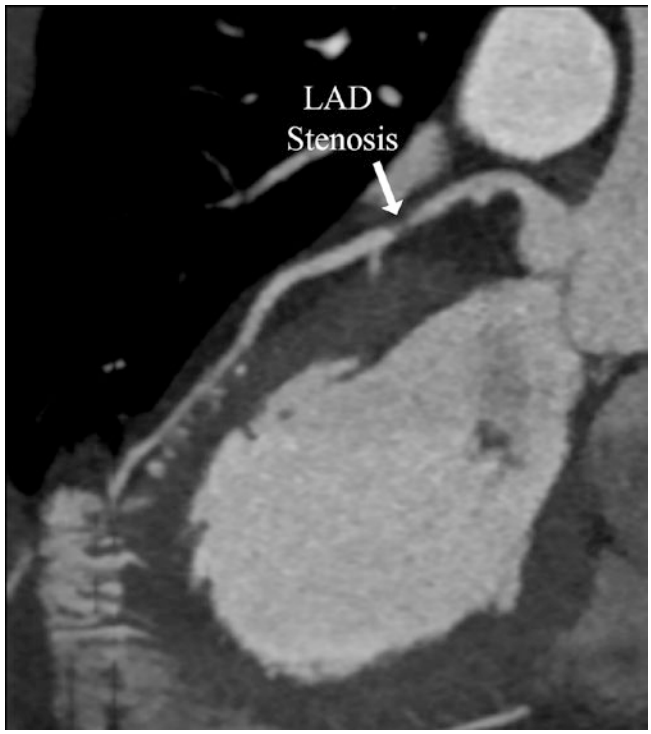


FIGURE 3-9

Severe stenosis in the left anterior descending artery (LAD) due to non-calcified plaque (arrow). Curved multi-planar reformat cardiac CTA image in a patient presenting with acute chest pain and low-intermediate pre-test probability of acute coronary syndrome without elevated cardiac biomarkers or ischemic ECG changes

CTA in the setting of prior test results

- Prior normal ECG exercise testing with continued symptoms, prior Duke Treadmill score with intermediate risk findings
- Discordant ECG exercise and imaging results, prior equivocal stress imaging procedure
- Evaluation of new or worsening symptoms in the setting of past normal stress imaging study
  - Meta-analysis shows good diagnostic accuracy for detection of obstructive CAD (≥50%) with sensitivity 98% and specificity 88% [3].
  - Due to high negative predictive values of 95–100%, coronary CTA has been used to "rule out" obstructive CAD in chest pain patients with low to intermediate risk of CAD.
  - CT delayed enhancement: myocardial scar detectable on non-contrast delayed enhancement scans, good concordance regarding the presence of late iodinated contrast enhancement in CT and cardiac magnetic resonance imaging (CMR) on a per-segment basis, though less sensitive than CMR.

Post revascularization (coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention)

- Evaluation of graft patency after CABG in **symptomatic** patients
  - CT ideal for graft assessment with high sensitivity (96%) and specificity (92%) [4].
  - Native coronary vessels are typically heavily calcified in this setting, limiting the diagnostic accuracy for stenosis evaluation.
- Localization of coronary bypass grafts and other retrosternal anatomy prior to reoperative chest or cardiac surgery
- Evaluation of left main coronary stent (diameter ≥3 mm) in **asymptomatic** patients

Assessment of adult congenital heart disease

- Coronary anomalies (Fig. 3-10)
- Anomalies of thoracic arteriovenous or aortic vessels (aorto-venous fistulas, aortic coarctation)
- Adult congenital heart disease (Figs. 3-3 and 3-11)

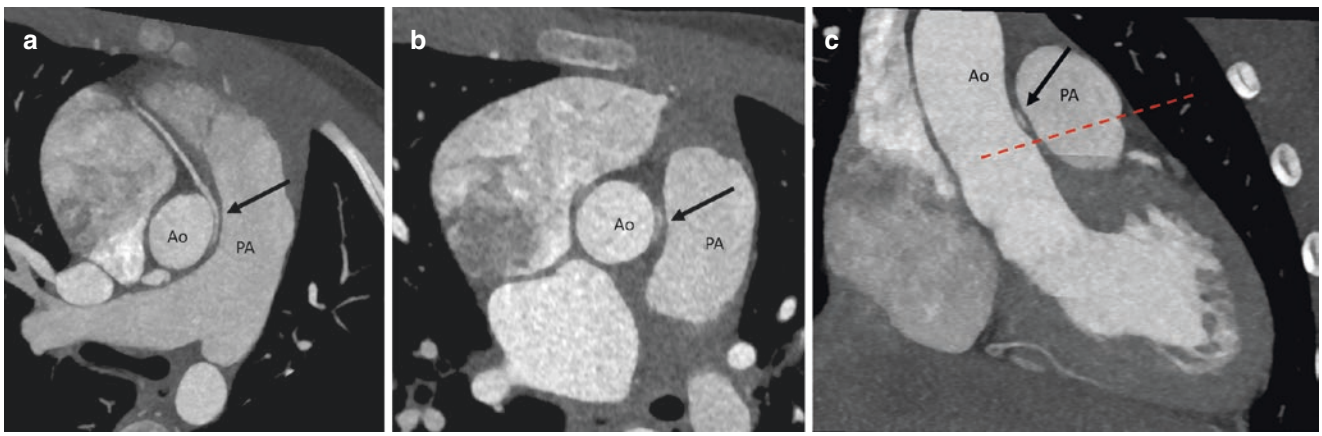


FIGURE 3-10

Anomalous high origin of right coronary artery from the ascending aorta (**a**). The proximal segment of RCA has a slit like appearance (**b**, **c**) which is characteristic of dysplastic intramural course. Also, the artery lies above the level of pulmonic annulus (dotted line, **c**) meaning that it's truly inter-arterial

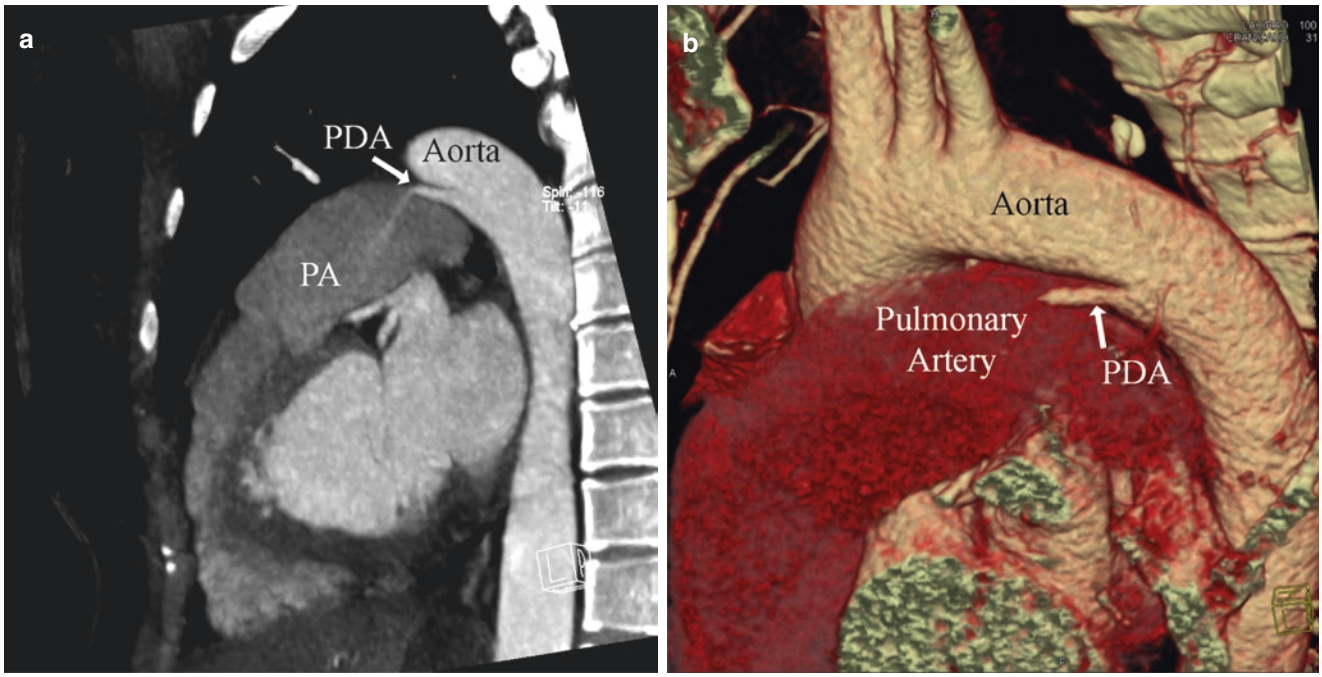


FIGURE 3-11

Patent ductus arteriosus (PDA). Cardiac CTA images (**a**, maximal intensity project; **b**, volume rendered image) demonstrating a PDA (arrow) with contrast traversing from the aorta to pulmonary artery (PA)

Assessment of ventricular morphology and function

- If other noninvasive methods like echocardiography or CMR are inadequate, CT can be used to evaluate of LV function following acute myocardial infarction or in heart failure patients.
- Quantitative evaluation of RV size and function, assessment of RV morphology (focal aneurysm), in suspected arrhythmogenic RV dysplasia

Pre-procedural planning for percutaneous valvular procedures

- CT provides evaluation prior to transcatheter aortic valve replacement to determine arterial measures for peripheral vascular access, aortic annulus size, aortic valve calcification and morphology, and distance from aortic annulus to coronary ostia.
- CT imaging can also be applied prior to valve-in-valve procedures in both the aortic and mitral positions. It is becoming a critical part of dedicated mitral annulus sizing for dedicated implantable mitral valves, although at the time of this writing none are approved for clinical use outside of trials.

Pre-procedural planning for electrophysiology procedures

- Evaluation of pulmonary vein and LA anatomy (Fig. 3-12)
  - Co-registration with electroanatomic mapping prior to pulmonary vein ablation
  - Assessment for LA appendage thrombus (Fig. 3-13), but confirmation with transesophageal echocardiography still required
- Evaluation of cardiac venous anatomy such as prior to biventricular pacemaker implantation (Fig. 3-14)

Evaluation of intra and extra cardiac structures

- If other imaging techniques are inadequate, CT can be used for characterization of native and prosthetic cardiac valves, and cardiac masses (e.g., tumors, thrombus).
  - CT is less sensitive for diagnosing valvular vegetations but useful for identifying paravalvular abscesses and pseudoaneurysms.

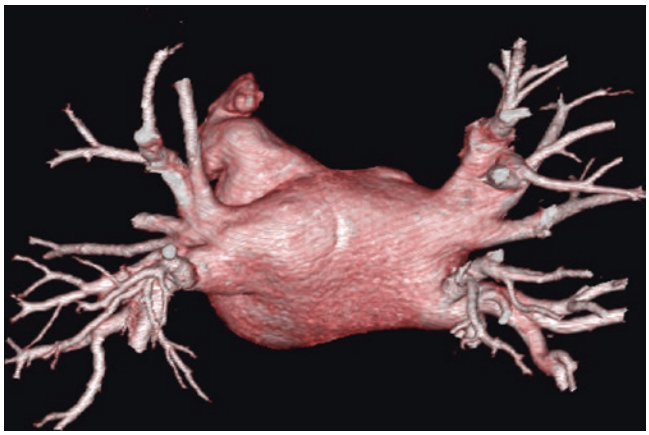


FIGURE 3-12

Pulmonary venous anatomy by CT prior to atrial fibrillation ablation. Volume rendered contrast-enhanced CT image showing the left atrium and pulmonary venous anatomy. This CT dataset is used to co-register with three-dimensional electroanatomic map in the electrophysiology laboratory for atrial fibrillation ablation

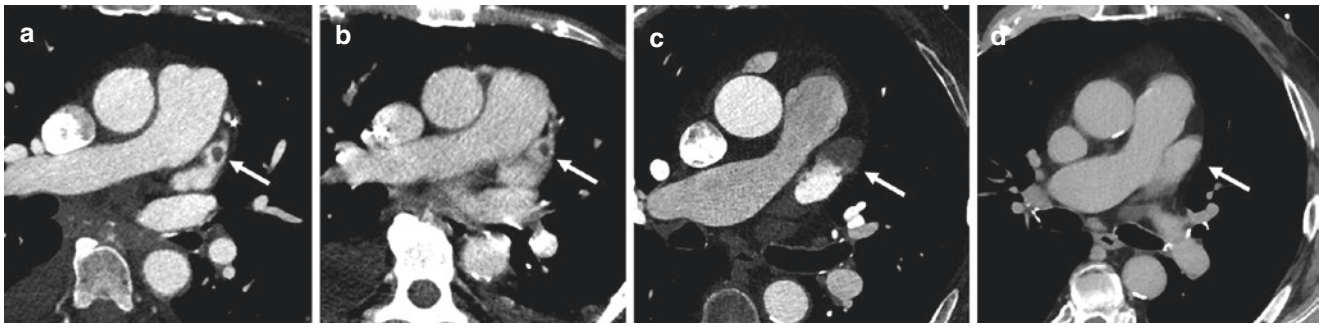


FIGURE 3-13

Left atrial appendage (LAA) thrombus. Contrast-enhanced cardiac CT shows a hypoattenuation filling defect in the LAA Small filling defect in the left atrial appendage on an arterial phase image (**a**) which persists on delayed image (**b**). On the contrary the filling defect on axial arterial phase image (**c**) from another patient does not persist on delayed image (**d**) and is consistent with slow flow phenomenon

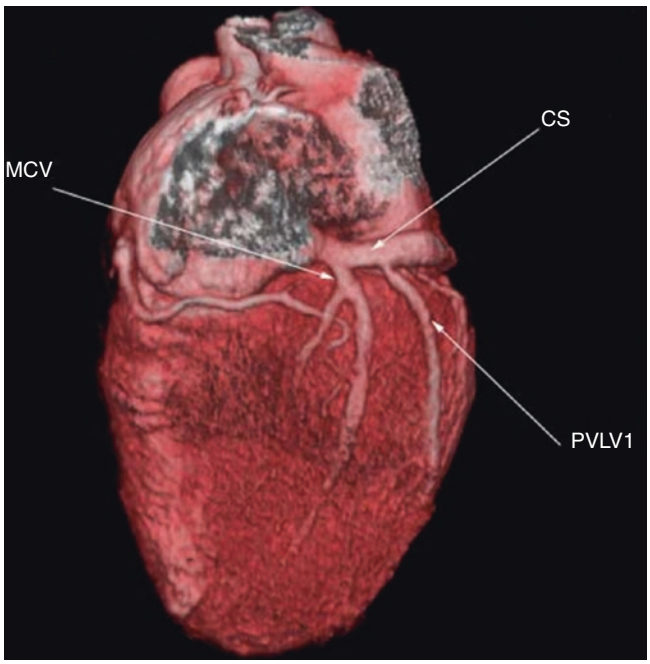


FIGURE 3-14

Cardiac venous anatomy by contrast-enhanced cardiac CT. Volume rendered CT image showing the cardiac venous system. CT venography may be used pre-procedurally to facilitate cardiac resynchronization therapy implantation. CS: coronary sinus, MCV: middle cardiac vein, PVLV1: first posterior vein to the left ventricle

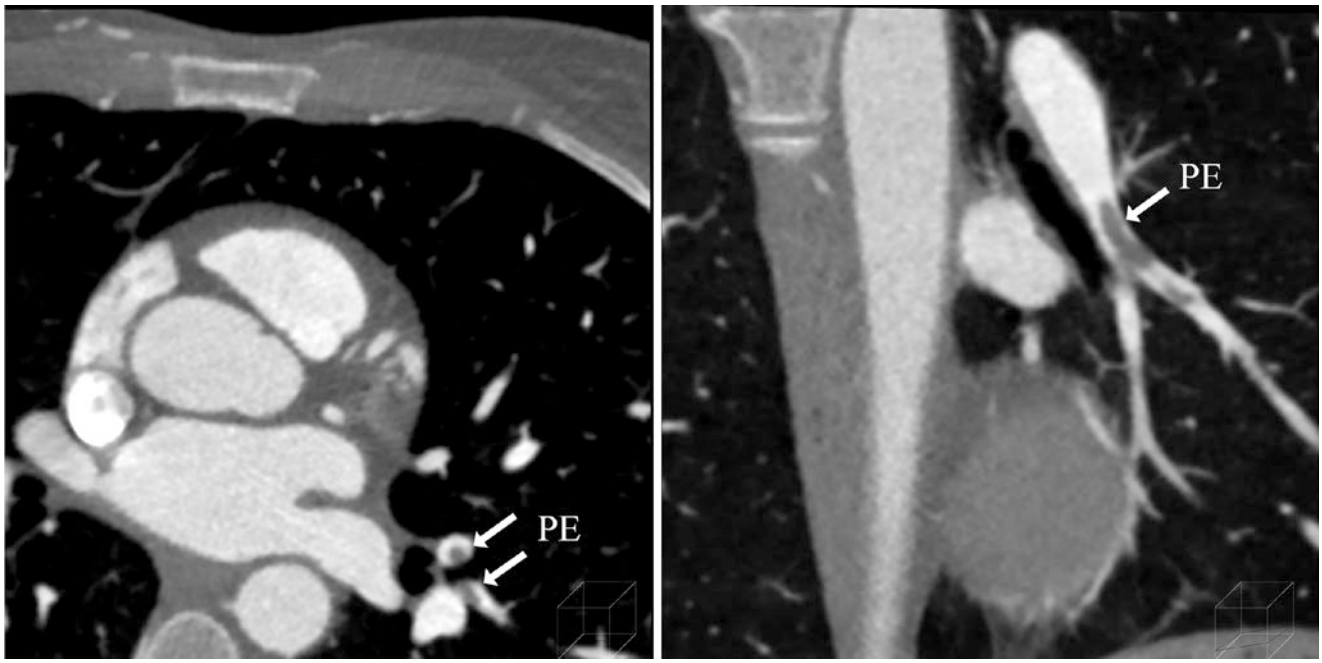


FIGURE 3-15

Pulmonary emboli (PE). Cardiac CTA images demonstrating the presence of PE (arrows) found incidentally in a patient presenting with acute chest pain

- Evaluation of pericardial anatomy
  - Pericardial effusions, thickening, fat, calcification (Fig. 3-5), tumors, cysts
  - CMR and echocardiography for constrictive physiology assessment
- Diagnosis of other non-cardiac pathologies
  - Thoracic aorta assessment: aortic aneurysms, dissection (Fig. 3-7), thoracic trauma, tears, intramural hematoma, mediastinal hematoma
  - Incidental findings: lung (pulmonary emboli (Fig. 3-15), pneumonia, nodules, effusion, atelectasis), liver (hemangiomas, cysts, tumor), bone (fractures, lytic lesions, degenerative disc disease), gastrointestinal (hiatus hernia, esophageal thickening), mediastinal lymphadenopathy, etc.

Medications in CT

Beta-blockers

- Given (if necessary) to reduce heart rate (HR), HR variability and ectopy to minimize motion artifact and allow accurate ECG-triggering (may be necessary if HR > 60–65 beats per minute, depending on scanner technology)

Sublingual or transdermal nitroglycerin

- If not contraindicated, it is administered for vasodilatory effects immediately prior (sublingual) or at least 40 min prior (transdermal patch) to coronary CTA. Diagnostic accuracy is reduced if nitroglycerin is not given.

Medications to avoid

- Metformin due to small potential risk of lactic acidosis from acute kidney failure related to contrast dye administration and should be held for 48 h following a scan.

CT Safety

Ionizing radiation

- Typical radiation doses are 0.3–3 mSv for a coronary calcium CT and 1–10 mSv for coronary CT angiography, depending on the technique and imaging system used.
- Adhere to the ALARA (As Low As Reasonably Achievable) principle regarding radiation with dose saving algorithms, minimization of repeated scans.
- **Stochastic effects**
  - These effects occur by chance and are not dependent on the radiation dose received. There is no lower threshold of radiation dose where it is certain that an adverse effect cannot occur. An example is the development of cancer in the future.
- **Non-stochastic or deterministic effects**
  - These effects are directly related to the radiation dose received with a clear relationship between dose and effect. For example, a large radiation dose may result in skin burns, hair loss, cataracts, sterility, gastrointestinal syndrome (eg. ulcers), or hematopoietic syndrome (eg. bone marrow suppression).

Side-effects related to iodinated contrast

- **Tissue extravasation**
  - Monitor for compartment syndrome and infection
- **Allergy**
  - Resulting in skin reactions (itch, rash) or anaphylaxis—prior history of mild contrast reaction (hives or less) requires premedication with steroid and anti-histamine prior to contrast administration
- **Contrast Induced Nephropathy**
  - Occurs when there is a temporal relationship between deterioration of renal function and the administration of intravenous contrast, in the absence of any other etiology
  - It can be defined as either a >25% increase of serum creatinine or an absolute increase in serum creatinine of 0.5 mg/dL after a radiographic examination using a contrast agent.
  - This condition occurs in <2% of patients, is very unlikely in patients with normal renal function (estimated glomerular filtration rate >60 mL/min/1.73 m^2), typically occurs 48 h post contrast, persists for 2–5 days and resolves by 7–10 days [5].

CARDIAC MAGNETIC RESONANCE (CMR) IMAGING

- CMR imaging uses magnetic and radiofrequency fields to generate signal from protons in hydrogen atoms.
- The typical magnetic field strengths used for clinical CMR are 1.5 and 3.0 Tesla.

Advantages and Disadvantages of CMR (Table 3-3)

CMR Scan Sequences

Dark Blood Imaging

- Flowing blood appears dark while slow moving structures such as myocardium is bright. T2-weighted images are sensitive to water content and will be represented as high signal in areas of acute injury such as myocarditis and infarction.

TABLE 3-3

ADVANTAGES AND DISADVANTAGES OF CMR

ADVANTAGES OF CMR	DISADVANTAGES OF CMR
High spatial (XY plane) and temporal resolution	Scanner availability and imager expertise
Imaging less affected by body habitus	Claustrophobia
No ionizing radiation	Contraindicated in patients with foreign metallic objects in eye or brain, and Starr-Edwards mechanical valve
Images can be acquired in any tomographic plane	Long image acquisition time
Increasingly available for most pacemaker and implanted defibrillator patients with monitoring	Gadolinium associated nephrogenic systemic fibrosis

Bright Blood Imaging

- This technique allows acquisition of cine images for assessment of cardiac function. Steady state free precession technique is commonly used for this purpose.

Phase-contrast

- Allows measurement of velocity and quantification of blood flow

Perfusion

- Contrast agents, such as gadolinium (Gd), that shorten T1 relaxation time can be imaged as they transit through cardiac structures.

Tissue mapping and Extracellular Volume (ECV) measurement

- Native properties of tissues are investigated to calculate the relaxation times of tissue before contrast (i.e. T1 and T2 "mapping"), or after contrast at several time points to quantitate the diffuse enhancement properties (ECV measurement). These quantitative measures can be compared to reference normal values to detect diffuse abnormalities that may not be apparent by traditional means

MR Angiography

- Rapid acquisition allows three-dimensional examination of complex cardiac and vascular structures

Late Gadolinium Enhancement

- Delayed hyperenhancement of Gd (~10 min after administration) is seen in areas of myocardial necrosis and fibrosis of many etiologies

CMR Indications [6]

Ischemic Heart Disease

- Vasodilator perfusion or dobutamine stress CMR in symptomatic patients is indicated with intermediate pre-test probability of CAD with uninterpretable ECG or inability to exercise.
- Stress perfusion to detect CAD can be performed with first-pass Gd perfusion imaging.
- Meta-analysis of 1516 patients demonstrated stress perfusion imaging with CMR has a sensitivity 91%, specificity 83% in detecting CAD (≥50% stenosis) [7].
- CMR parameters (LV ejection fraction, aortic flow, delayed enhancement) are incremental to perfusion data for predicting adverse outcomes [8].

Viability

- The degree of transmurality of late myocardial Gd enhancement is associated with the degree of myocardial viability [9].
- Myocardial segments with >50% transmural enhancement have a low likelihood of functional recovery after revascularization [10].

Cardiomyopathy

- CMR can provide accurate measurements of biventricular function, wall thickness, volume, and tissue characterization for diagnosis, management, and prognosis.
- It is appropriate to quantify LV function with CMR if echocardiographic imaging is technically limited or discordant with prior tests.

Ischemic Cardiomyopathy

- The pattern of abnormal late Gd enhancement follows a subendocardial through transmural gradient pattern, with its location in a specific coronary artery distribution (Table 3-4).

Non-Ischemic Cardiomyopathy

Myocarditis

- The presence of two CMR criteria for myocarditis has a sensitivity of 67% and specificity of 91% for the diagnosis of myocarditis [11].
  - Abnormal late Gd enhancement is typically subepicardial (focal or widespread)
  - Increased T2 signal suggesting myocardial edema (regional or global, Fig. 3-16)
  - Early global relative Gd enhancement indicating myocardial hyperemia and capillary leakage (Fig. 3-17)
  - T1 mapping and T2 mapping are proposed to supplant the relative qualitative measures traditionally used; these must be calibrated against normal for each scanner utilized.

Sarcoidosis

- The presence of abnormal late Gd enhancement can be in any non-ischemic distribution (Fig. 3-18) and is associated with subsequent adverse cardiac events [12].
- CMR has a sensitivity of 100% (78–100%) and specificity of 78% (64–89%) with an overall accuracy of ~80% in diagnosing cardiac sarcoidosis [13].

TABLE 3-4

DISTRIBUTION OF LATE GD ENHANCEMENT OF VARIOUS CARDIOMYOPATHIES AND PROGNOSTIC VALUE

CARDIOMYOPATHY	LV DISTRIBUTION	REGION	PROGNOSIS
Ischemic	Subendocardial, extending to transmural	Coronary artery distribution	>50% transmural=low likelihood of segmental functional recovery after revascularization
HCM	Midwall	Patchy, interventricular septum and junction	Independently associated with adverse outcome
Dilated	Midwall	Usually septal	Predicts death, CV hospitalization, VT
Myocarditis	Midwall, subepicardial	Variable Parvovirus B19: Lateral Herpes Virus 6: Septum	If lasting >4 weeks, associated with poor outcome
Amyloidosis	Subendocardial	Global (if subendocardial), patchy	Variable predicts HF severity, ± death
Sarcoidosis	Any (frequently midwall at the RV insertion site at the LV inferoseptum)	Any pattern	9-fold increase in adverse events and 11.5-fold increase in cardiac death
Anderson-Fabry	Epicardial/midwall	Basal inferolateral	Unknown
Endomyocardial fibrosis	Subendocardial	Inflow tract, Apex	11-fold increase in mortality
Chagas disease	Epicardial/midwall	Inferolateral/apex	Unknown

CV cardiovascular, *HCM* hypertrophic cardiomyopathy, *HF* heart failure, *HR* hazard ratio, *LV* left ventricular, *RV* right ventricular, *VT* ventricular tachycardia

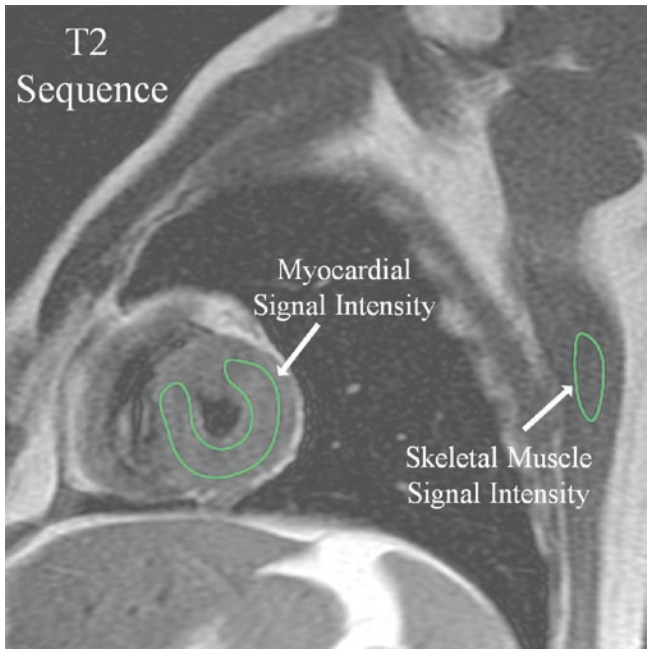


FIGURE 3-16

CMR T2 assessment for myocarditis. Offline measurement for increased global T2 myocardial enhancement corrected for skeletal muscle, which is one parameter for assessment of myocarditis

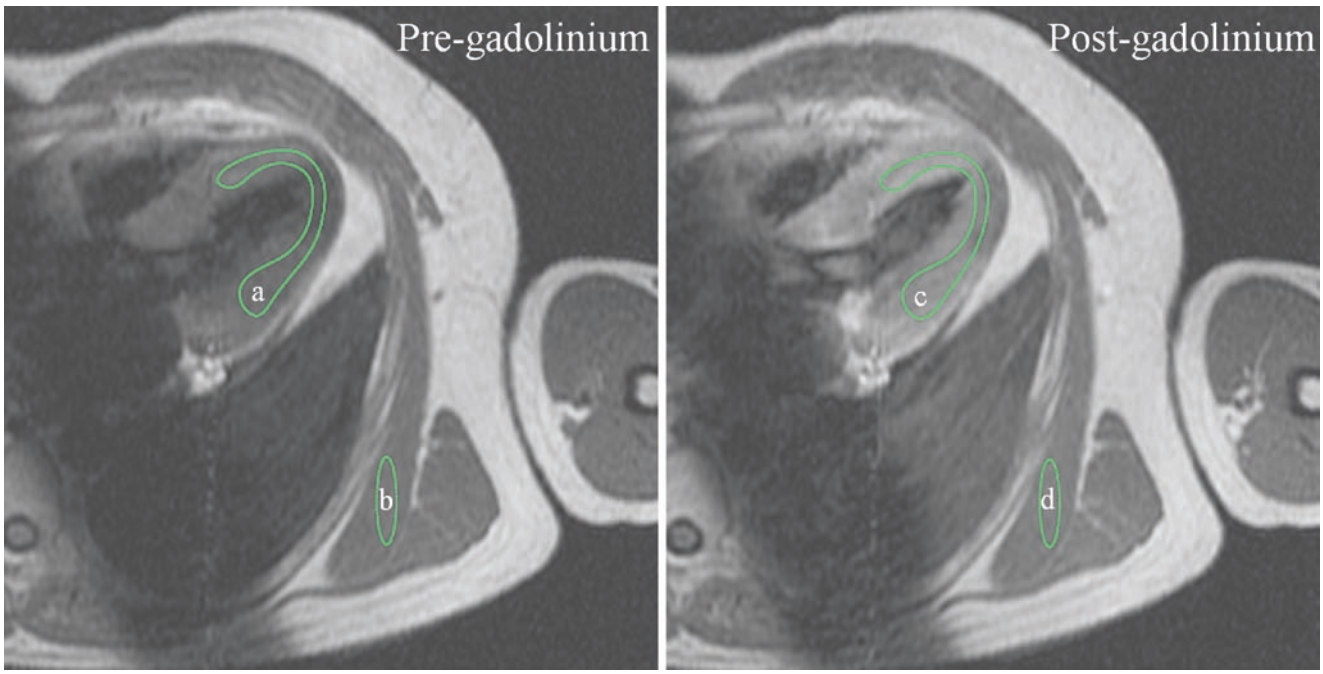


FIGURE 3-17

CMR early global relative gadolinium (Gd) assessment for myocarditis. Offline measurement comparing the pre- and post-Gd images. The ratios of pre-Gd myocardial: skeletal muscle (**a**/**b**) are compared to the post-Gd myocardial: skeletal muscle (**c**/**d**) signal intensities

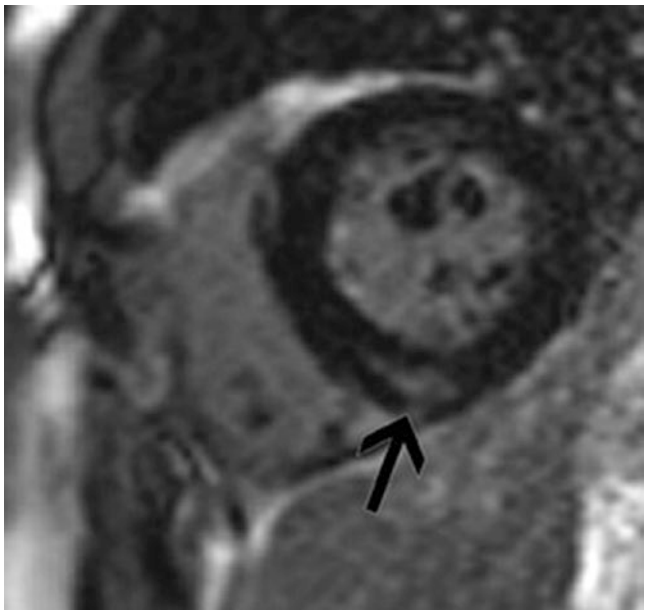


FIGURE 3-18

Cardiac sarcoidosis. CMR delayed enhancement of the left ventricular short-axis at the mid-ventricular level showing patchy, myocardial scarring in the inferior septum (arrow) in a patient with known systemic sarcoidosis

Amyloidosis

- Global transmural or subendocardial left and right ventricular late Gd enhancement is the typical finding on CMR and corresponds to the histological distribution of amyloid protein [14].
- Increased T1 signal in comparison to controls and other pathologies is predictive of mortality.

Hypertrophic cardiomyopathy

- CMR is able to identify increased regional wall thickness not appreciated on other imaging techniques as well as accurate quantification of left ventricular mass.
- Various patterns of late Gd enhancement, representative of fibrosis, are identified in patients with hypertrophic cardiomyopathy (Fig. 3-19) and are shown to be associated with adverse prognosis, especially when involving >15% of the LV mass [15].
- Late Gd enhancement alone is not widely considered adequate to justify defibrillator implantation but is increasingly factored into challenging decisions, particularly if meeting the 15% mass threshold.

Hemochromatosis

- $T2^*$ measurement of myocardium on CMR can be used to identify subjects with cardiac involvement in hemochromatosis, with a $T2^*$ of less than 20 ms is associated with left ventricular systolic dysfunction [16].

Arrhythmogenic Right Ventricular Dysplasia

- Quantitative evaluation of RV size and function, assessment of RV morphology (focal aneurysm) in suspected arrhythmogenic RV dysplasia
- Fatty deposition and fibrosis in the RV by CMR are not part of the modified Task Force criteria [17]

Non-compaction cardiomyopathy

- A diastolic ratio of non-compacted (trabeculated) to compacted myocardium of greater than 2.3 has a sensitivity of 86% and specificity of 99% for diagnosing non-compaction cardiomyopathy [18].

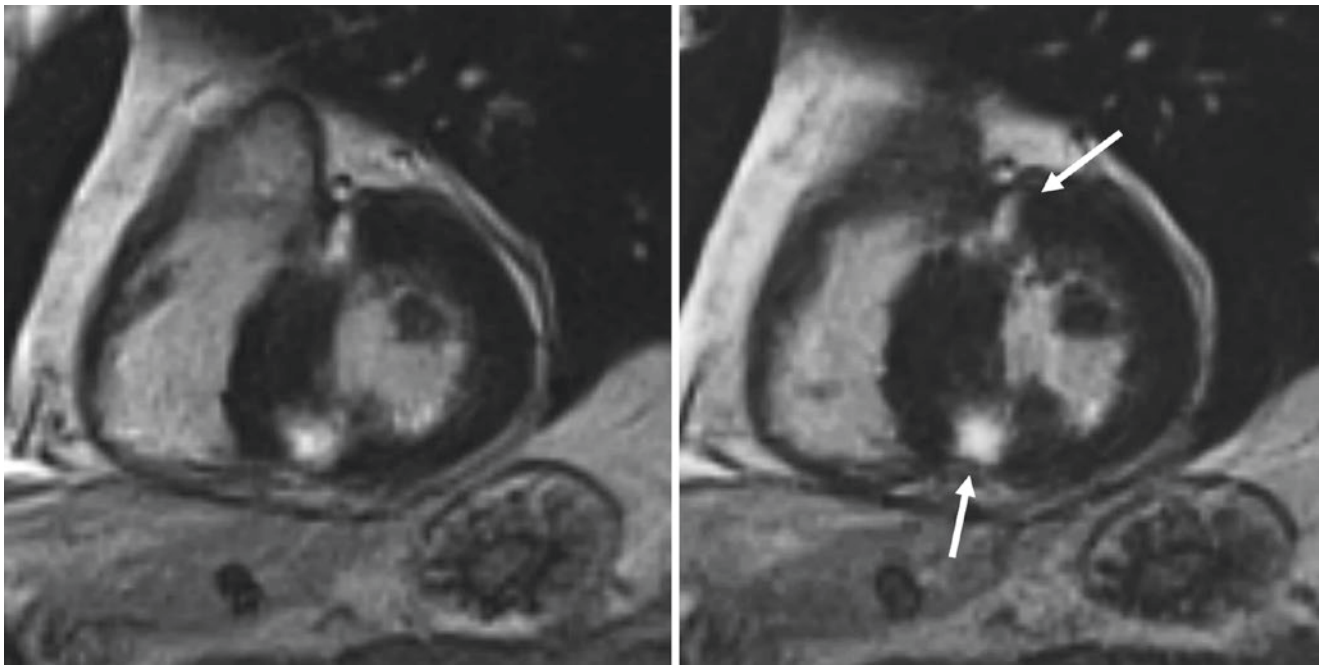


FIGURE 3-19

Hypertrophic cardiomyopathy with midwall delay gadolinium enhancement of the left ventricle (LV) which is associated with increased risk for sudden cardiac death. Note the thick myocardial wall. RV: right ventricle

Anderson-Fabry Disease

- Late Gd enhancement characteristically involves the basal and mid anterolateral and inferolateral walls and usually spares the subendocardium.
- Can occur in the presence or absence of LVH

Congenital Heart Disease

- Quantification of LV and RV mass, volume and ejection fraction
- Quantification of valvular disease
- Assessment of great vessels, coronary anomalies, flow through surgical conduits
- Specific indications for CMR in congenital heart disease
  - Shunt size (Qp/Qs) calculation with phase contrast imaging
  - Assessing anomalous pulmonary and systemic venous return
  - Aortic abnormalities (e.g., coarctation (Fig. 3-5b), aortic aneurysm)
  - Pulmonary artery abnormalities (e.g., pulmonary atresia, stenosis)
  - Systemic to pulmonary collateral
  - Complex congenital disease assessment and surgical follow-up (i.e., post atrial/arterial switch operation for transposition of great arteries, Fontan operations and post-Tetralogy of Fallot repair)

Cardiac Tumor

- CMR is an excellent modality for visualization and characterization of cardiac masses.
- The main advantages of CMR include better contrast resolution, multiplanar capability, ability to assess functional impact of the tumor, tissue characterization and detection of vascularity of the tumor with first pass perfusion imaging.
- Differentiates intracardiac thrombus from tumor and benign from malignant cardiac masses (Fig. 3-20)

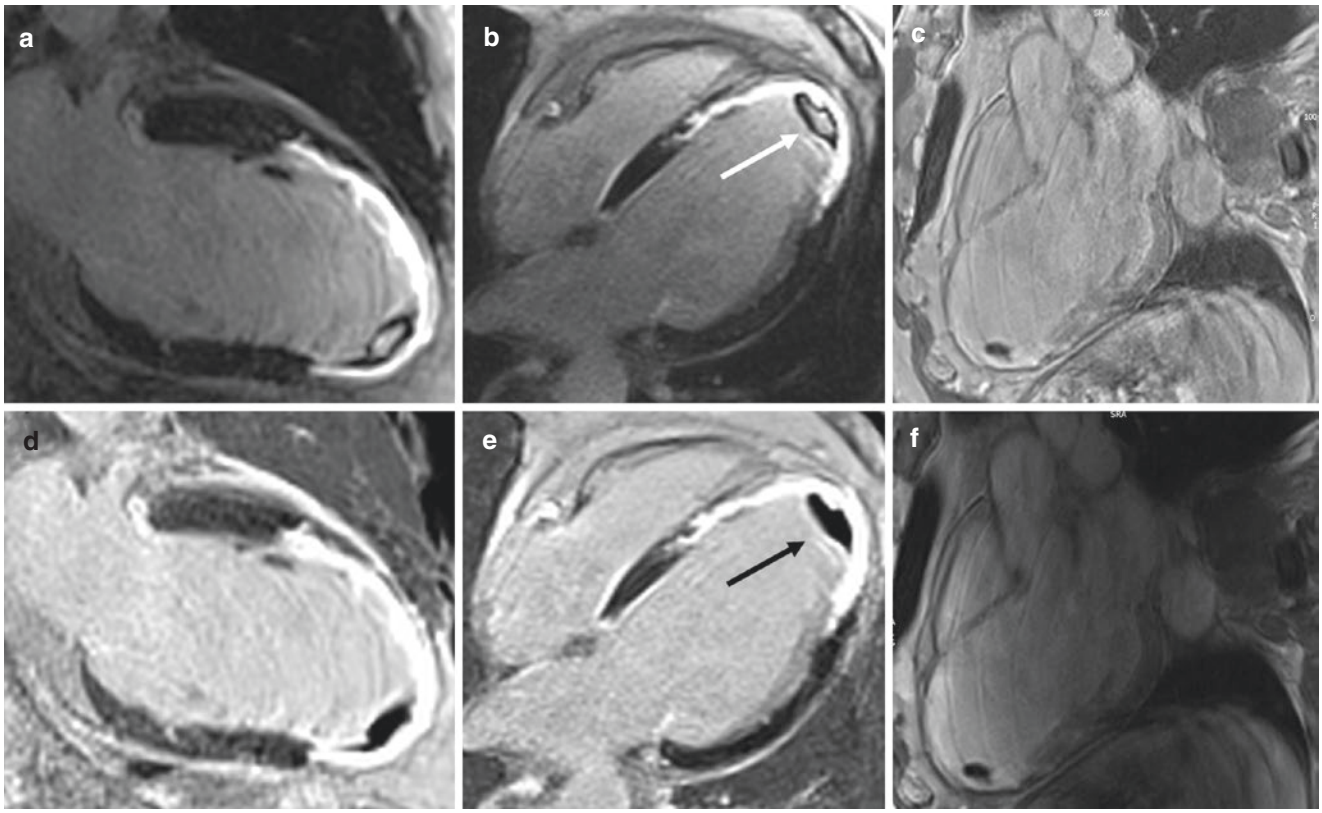


FIGURE 3-20

Apical infarct and thrombus. Magnitude (top panel) and phase sensitive (bottom panel) images demonstrate subendocardial to transmural late gadolinium enhancement in territorial distribution (LAD infarct). A small intracavitary mass lesion at infarcted apex is a thrombus (**a**, **b**) which is hypointense on PSIR images at shorter inversion time (**d**, **e**) and also remains hypointense on longer inversion time (500 ms; **c** & **f**)

Pericardial disease [19]

- Assessment of pericardial disease such as pericardial mass and pericardial constriction
- Features of pericardial constriction on CMR: thickened pericardium ≥4 mm, paradoxical motion of the interventricular septum, lack of normal breaking of tag lines on tagging sequence during cardiac contraction due to shear motion between visceral and parietal pericardium (Fig. 3-21), calcified pericardium

Valvular heart disease

- If other forms of imaging such as echocardiography is technically limited, CMR can assess valvular function.
- Qualitative assessment of regurgitant and stenotic jets can be seen on cine CMR.
- Quantitative assessment of stenosis can be measured by planimetry or using phase contrast sequences to determine peak velocity across the valve.
- Regurgitant volume and fraction can be assessed by phase contrast sequences (determining the forward and reverse flow) or (sometimes) by assessing the differences in RV and LV stroke volume.

Evaluation of pulmonary vein and left atrial (LA) anatomy

- Co-registration with electroanatomic mapping prior to pulmonary vein ablation

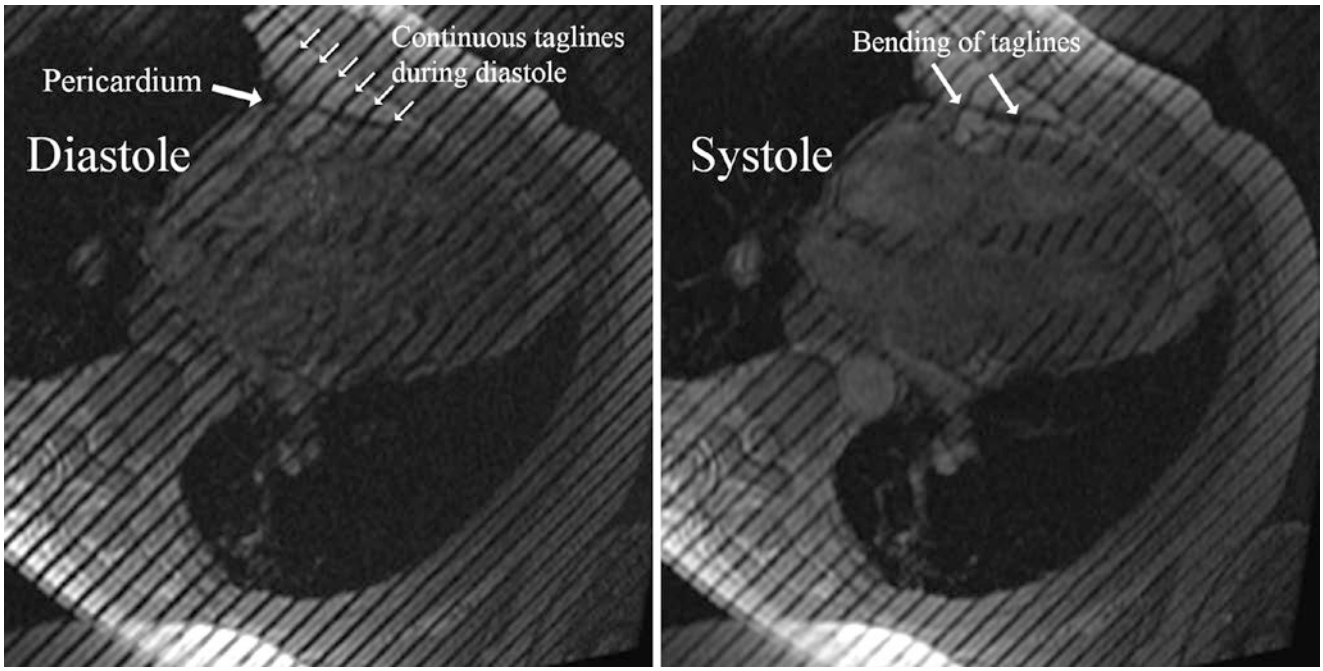


FIGURE 3-21

Pericardial constriction. Tagging CMR sequences showing unbroken taglines over the pericardium during ventricular diastole and *bending* of taglines over the pericardium during systole suggesting pericardial adhesions

CMR Safety

- The use of Gd in end-stage renal patients is associated with a rare but serious complication of *nephrogenic systemic fibrosis*, which result in fibrosis of skin overlying the extremities and truck and deeper structures including muscle, lung and heart.
- Ferromagnetic implants may lead to complications with CMR and should be screened prior to CMR [20].
- It is generally recommended a waiting period of about 6 weeks post implantations of weakly ferromagnetic devices (e.g., cardiac valves and stents) before CMR.
- CMR in patients with pacemaker and implantable cardioverter-defibrillator can potentially lead to heating of the tip of the lead, inhibiting pacing output, activating tachyarrhythmia therapy or damage to the device.
- CMR-compatible pacemaker systems have recently become available, and these individuals are now able to safely undergo imaging with appropriate monitoring and careful adjustment of the exam parameters to ensure acquisitions remain within prescribed limits of gradient strengths and power deposition.

Questions and Answers

1. Per the 2010 Appropriate Use Criteria for cardiac computed tomography (CT), which of the following is false?
   A) It is appropriate to perform a CT calcium score in an asymptomatic patient with intermediate pretest probability of coronary artery disease
   B) It is appropriate to perform CT angiography in an asymptomatic patient with intermediate pretest probability of coronary artery disease
   C) It is appropriate to perform CT angiography in a patient with acute chest pain intermediate pretest probability of coronary artery disease with normal ECG and cardiac biomarkers
   D) It is appropriate to perform CT angiography for risk assessment in an asymptomatic patient with prior 3.5 mm left main stent
   E) It is appropriate to perform CT angiography in a symptomatic patient with intermediate pretest probability of coronary artery disease with interpretable ECG and able to exercise

   1. Answer: B. Non-contrast calcium score is used for risk assessment in asymptomatic patients without known coronary artery disease (CAD). It is inappropriate for coronary CT angiography to be performed for risk assessment in asymptomatic patients with no previous coronary artery disease with low to intermediate pretest probability of CAD.

2. What artificial valve is shown in this CXR (Fig. 3-22)?
   A) Mechanical mitral valve
   B) Mechanic aortic valve
   C) Bioprosthetic aortic valve
   D) Mechanical tricuspid valve
   E) Bioprosthetic mitral valve

   2. Answer E. The CXR demonstrates a bioprosthetic mitral valve with the perceived direction of flow is towards the apex.

3. A 59-year-old man who presented with symptoms of heart failure after mediastinal irradiation for Hodgkin lymphoma undergoes cardiac magnetic resonance (CMR) imaging. Which of the following feature is NOT consistent with pericardial constriction on CMR?
   A) Pericardial thickness ≥4 mm
   B) Left ventricular myocardial trabeculation ratio >2.3
   C) Lack of normal breaking of tag lines during cardiac contraction
   D) Pericardial calcification
   E) Septal flattening on early diastolic filling

   3. Answer B. The ratio of noncompacted to compacted left ventricular (LV) myocardium of >2.3 is consistent with LV noncompaction, which is not a feature of pericardial constriction.

4. Which of the following complications does not occur with CT angiography?
   A) Nephrogenic systemic fibrosis
   B) Anaphylaxis
   C) Compartment syndrome of the arm
   D) Contrast induced nephropathy
   E) Bradycardia

   4. Answer A. Nephrogenic system fibrosis is a potential complication of gadolinium administration when undergoing cardiac magnetic resonance (CMR) imaging. Anaphylaxis and contrast induced nephropathy are potential complications of iodinated contrast administration used in cardiac computed tomography (CT), severe tissue extravasation of iodinated contrast may result in compartment syndrome of the arm and beta-blockers administered prior to coronary CT angiography can result in bradycardia.

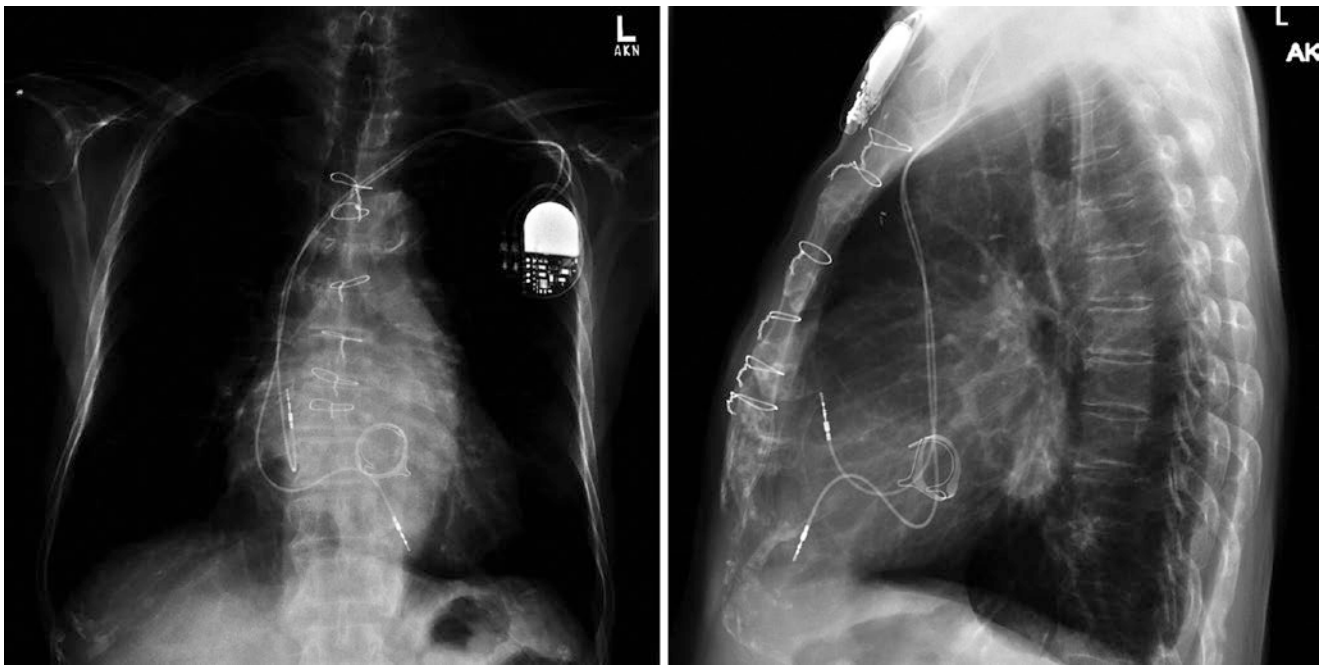


FIGURE 3-22

Frontal and lateral CXR images for question 2

5. Which of the following is a stochastic effect from ionizing radiation?
   A) Radiation burns
   B) Cancer
   C) Permanent sterility
   D) Radiation sickness
   E) Cataracts

   5. Answer: B. Stochastic effects occur by chance and are not dependent on the radiation dose received (e.g., cancer). There is also no lower threshold of radiation dose where it is certain that an adverse effect cannot occur. The other options are examples of non-stochastic effects, which are effects that are directly related to the radiation dose received; there is a clear relationship between radiation dose and non-stochastic effect.

6. A 52-year-old woman with hypertension and dyslipidemia presents to the emergency department with worsening chest discomfort on minimal exertion. Her ECG was non-diagnostic and two sets of troponin were negative. She underwent coronary computed tomography (CT) angiography. This image (Fig. 3-23) demonstrates:
   A) Anomalous left coronary artery arising from the right Sinus of Valsalva with an interarterial course
   B) Severe aortic regurgitation due to aortic dissection
   C) Severe stenosis in the mid right coronary artery
   D) Sinus venosus atrial septal defect
   E) Unroofed coronary sinus

   6. Answer: C. This CT image demonstrates severe stenosis in the mid right coronary artery due to non-calcified plaque.

7. A 60-year-old man with type 2 diabetes on metformin and hypertension presents with dyspnea and impaired left ventricular systolic function on echocardiography. Based on the delayed gadolinium enhancement on cardiac magnetic resonance (CMR) imaging (Fig. 3-24), what is the most likely cause of the systolic dysfunction?
   A) Myocarditis
   B) Amyloid
   C) Previous left anterior descending artery territory myocardial infarction
   D) Previous right coronary artery territory myocardial infarction
   E) Constrictive pericarditis

   7. Answer: C. The subendocardial distribution of late gadolinium enhancement in the anterior wall on CMR is consistent with previous anterior myocardial infarction. The typical late gadolinium enhancement seen in myocarditis is subepicardial. Cardiac amyloid typically has global subendocardial delayed enhancement, rather than localizing to a coronary distribution. The following diagram (Fig. 3-25) illustrates the distribution of late gadolinium enhancement in various cardiac conditions.

8. A 35-year-old man with back pain has the above finding on computed tomography (CT) (Fig. 3-26), which of the following is false?
   A) He may have an autosomal dominant genetic disorder
   B) He may have a diastolic and systolic murmur on examination
   C) He requires urgent surgical consultation
   D) He has non-compaction of the left ventricle
   E) He may have a mutation of the transforming growth factor beta receptor 1

   8. Answer: D. This gentleman has a dilated aortic root and left ventricle. He may have Marfan's syndrome which is an autosomal dominant genetic disorder, however patients with Loeys-Dietz syndrome may also have aortic aneurysms due to a mutation of the gene encoding transforming growth factor beta receptor 1. Urgent surgical intervention is required in patients with an aortic diameter of 5 cm, however in patients with Marfan's or Loeys-Dietz syndrome, earlier intervention is recommended at 4 cm. On CMR, the ratio of noncompacted to compacted myocardium of 2.3 has good accuracy for the detection of non-compaction. A similar ratio has been applied to properly-acquired cardiac CT and validated versus MRI. However, the patient in this scenario does not have non-compaction, as the diagnosis of non-compaction cardiomyopathy requires the absence of other etiologies of left ventricular wall thickness abnormalities and/or dysfunction.

9. A 47-year-old man presents for CTA to investigate first presentation of intermittent chest discomfort. He is a current smoker and has a history of diabetes on metformin, dyslipidemia on atorvastatin, erectile dysfunction on vardenafil and benign prostatic hypertrophy. On examination, his heart rate is 79 beats per minute, he has a harsh ejection systolic murmur which becomes louder with the Valsalva maneuver and clear lung fields. Which of the following is not advised when performing CTA for this patient?
   A) Withhold metformin for 48 h post CTA
   B) Administration of metoprolol to achieve heart rate of 60–65 beats per minute
   C) Administration of iodinated contrast for the coronary CTA
   D) Administration of sublingual nitrates for coronary vasodilation to improve CTA accuracy
   E) All the above can be advised or given

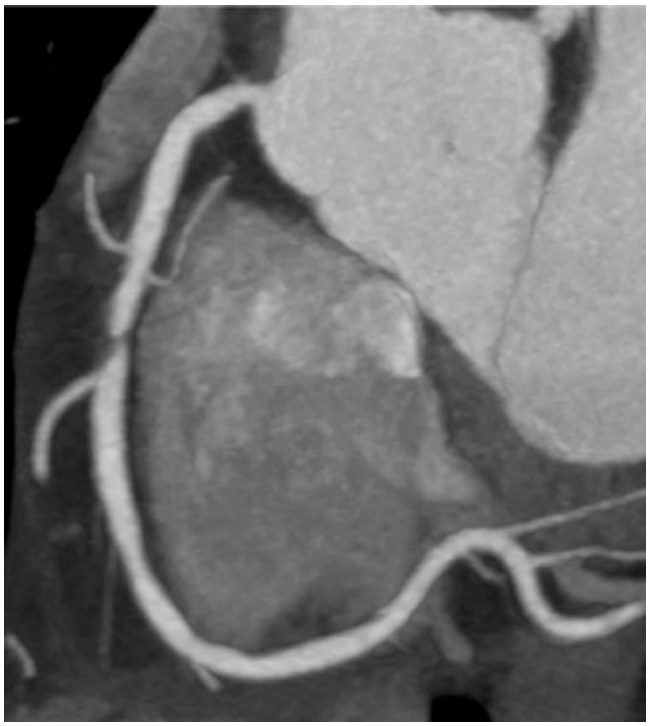


FIGURE 3-23

Curved multiplanar reformatted coronary CT angiography image for question 6

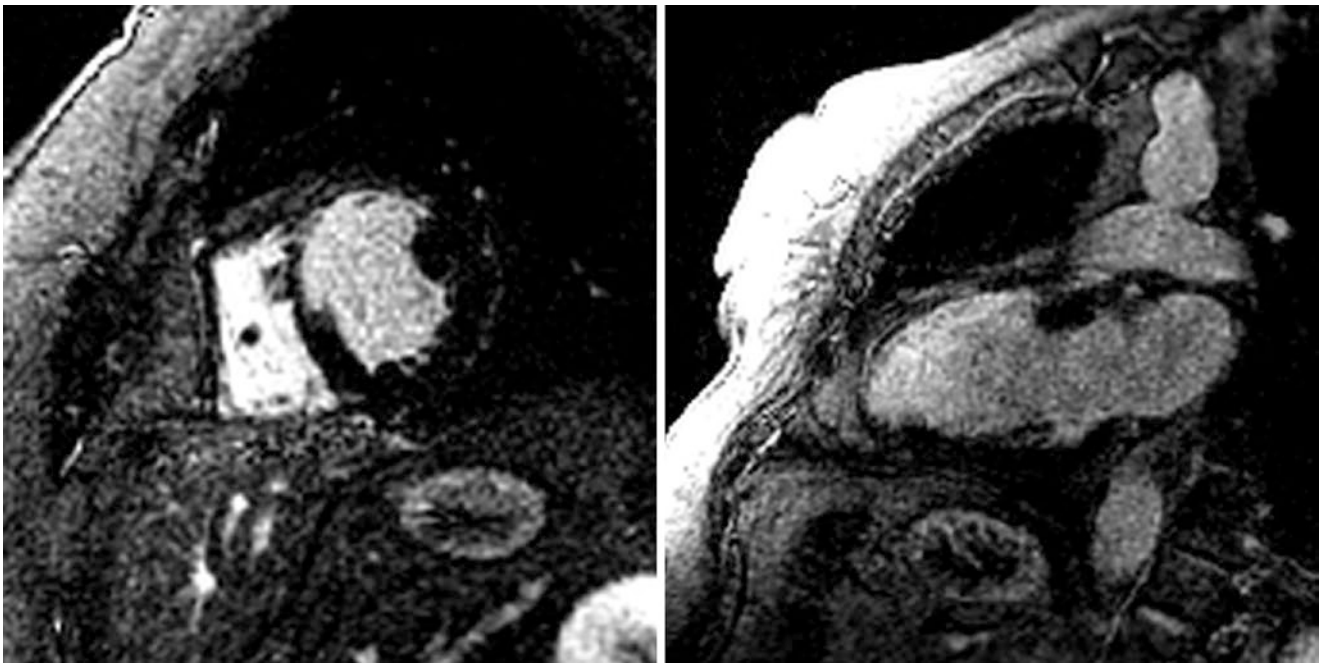


FIGURE 3-24

Short and long axis CMR images of late gadolinium enhancement for question 7

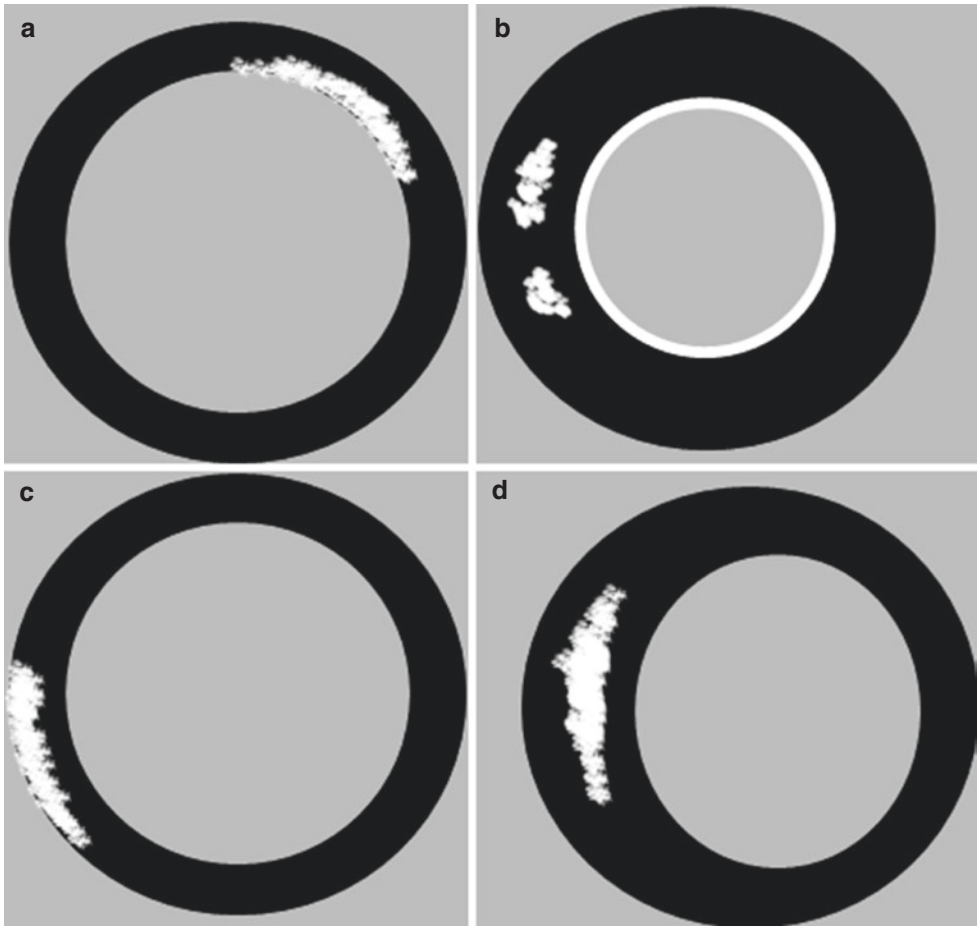


FIGURE 3-25

Late gadolinium enhancement in various cardiovascular conditions. (**a**) Ischemic heart disease (subendocardial enhancement), (**b**) Amyloid cardiomyopathy (global enhancement), (**c**) Myocarditis (subepicardial enhancement), and (**d**) Hypertrophic cardiomyopathy (mid-wall enhancement)

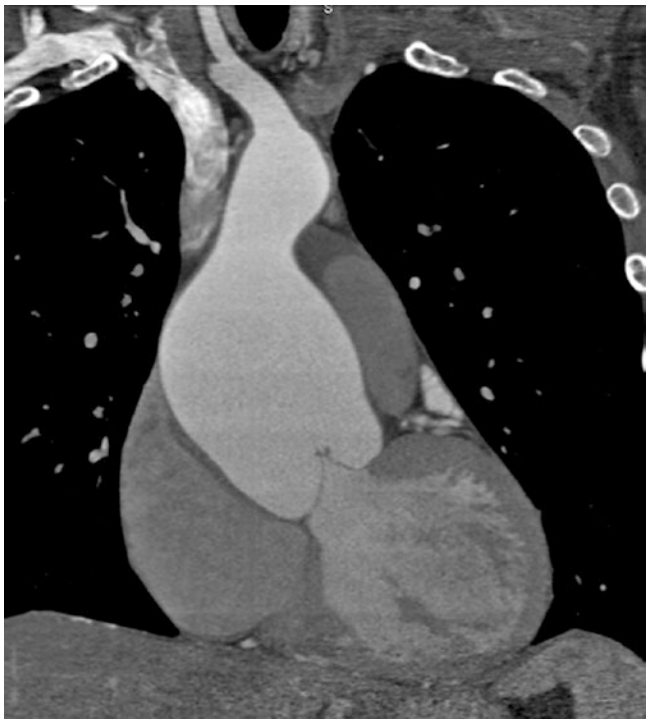


FIGURE 3-26

Coronal CT angiography image for question 8

9. Answer: D. The administration of nitroglycerin (400–800 μg of a sublingual tablet or sublingual spray) is performed immediately prior to coronary CTA to improve diagnostic accuracy by causing vasodilation of the coronary arteries. The patient in this scenario has clinical signs which may be due to hypertrophic obstructive cardiomyopathy and is taking a 5-phosphodiesterase type 5 inhibitor (vardenafil). Nitroglycerin should be avoided in patients with hypertrophic cardiomyopathy with outflow tract obstruction or severe aortic stenosis as nitrates many reduce preload, exacerbate obstruction and result in hypotension, syncope or worsening heart failure. Nitroglycerin should also be avoided in patients on PDE-5 inhibitors.

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CHAPTER 4

NEEL M. BUTALA, FAROUC A. JAFFER, AND MARC S. SABATINE

Acute Coronary Syndrome

CHAPTER OUTLINE

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
AS	Aortic stenosis
ASA	Aspirin
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
CTA	Computerized tomographic angiography
CPR	Cardiopulmonary resuscitation
DAPT	Dual antiplatelet therapy
DM	Diabetes mellitus
ECG	Electrocardiogram
FFR	Fractional flow reserve
GP IIb/IIIa	Glycoprotein IIb/IIIa
HR	Heart rate
ICD	Implantable cardioverter defibrillator
IV	Intravenous
LBBB	Left bundle branch block
LDL-C	Low density lipoprotein cholesterol
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MR	Mitral regurgitation
NSTEMI	Non-ST-elevation myocardial infarction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin kexin 9
RBBB	Right bundle branch block
RV	Right ventricle
SBP	Systolic blood pressure
SC	Subcutaneous
SCAD	Spontaneous coronary artery dissection
STEMI	ST-elevation myocardial infarction

TIA	Transient ischemic attack
UA	Unstable angina
UFH	Unfractionated heparin
VSR	Ventricular septal rupture
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Coronary artery disease (CAD) is a major cause of mortality and morbidity in the United States and worldwide. In 2018, the American Heart Association reported that 16.5 million individuals in the United States had coronary artery disease, and that 720,000 individuals will have a new coronary event, with 355,000 of those classified as a recurrent coronary event [1].

DIAGNOSIS (SEE TABLE 4-1)

A) **History and Physical Examination** *(see Chap. 1)*

- There is often a broad range of presenting discomfort features and associated symptoms, particularly in women, older patients, young patients, diabetics, and those with renal insufficiency.
- Substernal chest discomfort is typically pressure-like and occurs at rest or with increasing frequency, lasting for several minutes, and often with relieved by nitroglycerin. It may radiate to the neck, arms, shoulder, and/or jaws. Ischemic chest discomfort is often associated with dyspnea, diaphoresis, nausea, and/or vomiting [3, 4]. Less typical features may include fatigue and back pain, and the *absence* of chest discomfort.
- Physical exam features that suggest a high likelihood of acute coronary syndrome (ACS) include diaphoresis, hypotension or shock, S3 gallop, transient mitral regurgitation (MR), and pulmonary edema [3].
- Differential diagnosis of chest pain [3].
  - ACS
  - Non-atherosclerotic coronary causes: dissection, spasm, embolism, severe microvascular dysfunction, supply-demand inequity, vasculitis, cardiac allograft vasculopathy
  - Other cardiovascular: aortic dissection, expanding aortic aneurysm, pericarditis, myocarditis, stress-mediated cardiomyopathy, pulmonary embolism, pulmonary hypertension, myocardial contusion
  - Gastrointestinal: esophageal (gastroesophageal reflux, esophageal spasm, esophagitis), gastric (gastritis, peptic ulcer disease), biliary (cholecystitis, cholelithiasis), pancreatitis
  - Musculoskeletal: trauma, costochondritis, Tietze syndrome (inflammation of costal cartilages), fibromyalgia
  - Pulmonary: pneumonia, malignancy, pneumothorax, pleuritis, pleural effusion
  - Neuropathic: herpes zoster, postherpetic neuralgia, radiation, radiculopathy
  - Psychiatric: panic disorder, hypochondriasis, malingering

B) **Electrocardiogram**

- Normal ECG (electrocardiogram) carries a favorable prognosis but does not rule out ACS. *Nearly 50% of patients presenting with UA (unstable angina)/NSTEMI (non-ST-elevation myocardial infarction) have a normal or unchanged ECG*. ECG should be repeated at 15- to 30-min intervals for first hour or if continued pain if initial ECG is not diagnostic [3].

TABLE 4-1

LIKELIHOOD THAT SIGNS AND SYMPTOMS REPRESENT AN ACS SECONDARY TO CAD

FEATURE	HIGH LIKELIHOOD	INTERMEDIATE LIKELIHOOD	LOW LIKELIHOOD
	Any of the following:	*Absence of high-likelihood features and presence of any of the following:*	*Absence of high- or intermediate-likelihood features but may have:*
History	■ Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina ■ Known history of CAD, including MI	■ Chest or left arm pain or discomfort as chief symptom ■ Age > 70 yo ■ Male sex ■ DM	■ Possible ischemic symptoms in absence of any of the intermediate likelihood characteristics ■ Recent cocaine use
Exam	■ Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	■ Extracardiac vascular disease	■ Chest discomfort reproduced by palpation
ECG	■ New, or presumably new, transient ST-segment deviation (1 mm or greater) or T-wave inversion in multiple precordial leads	■ Fixed Q waves. ■ ST depression 0.5–1 mm or T-wave inversions >1 mm	■ T-wave flattening or inversion <1 mm in leads with dominant R waves ■ Normal ECG
Cardiac markers	■ Elevated cardiac TnI, TnT, or CK-MB	■ Normal	■ Normal

Adapted from: Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007 Aug 14;50(7):e1–e157 [2]

ACS acute coronary syndrome, *CAD* coronary artery disease, *CK-MB* creatine kinase-MB, *DM* diabetes mellitus, *ECG* electrocardiogram, *MI* myocardial infarction, *MR* mitral regurgitation, *TnI* troponin I, *TnT* troponin T

■ UA/NSTEMI

– New T wave inversions >0.2 mV and ≥0.05 mV ST depressions are suggestive [3].
– Presence of ischemic changes in setting of right bundle branch block (RBBB) is poor prognostic sign [5, 6].

■ STEMI (ST-elevation myocardial infarction): New ST elevations at the J-point in ≥2 contiguous leads ≥1 mm in all leads other than leads V2-V3 and ≥2 mm in men ≥40 years, ≥2.5 mm in men <40 years, or ≥1.5 mm in women in leads V2-V3 (in absence of left ventricular hypertrophy or LBBB) [7].

– Posterior MI (myocardial infarction; Fig. 4-1a–c): ST depression V1 and V2 (particularly if horizontal ST depression with upright T wave and tall R wave) and/or ST elevation on posterior leads V7-V9 [8].

■ Approximately 4% of acute MI patients have isolated posterior ST elevations; detecting the presence is important since it qualifies for acute reperfusion therapy. Posterior ECG leads should be obtained.

– RV (right ventricular) MI

■ If inferior STEMI, perform right-sided leads to evaluate for RVMI
■ ST elevation ≥1 mm in V1 (sensitivity 28%, specificity 92%), and/or V_4R (sensitivity 93%, specificity 95%) [9].

– New 1–3 mm upsloping ST depression at the J point in leads V1-V6 with tall, positive symmetrical T-waves (de Winter's sign) suggestive of proximal LAD occlusion [10]

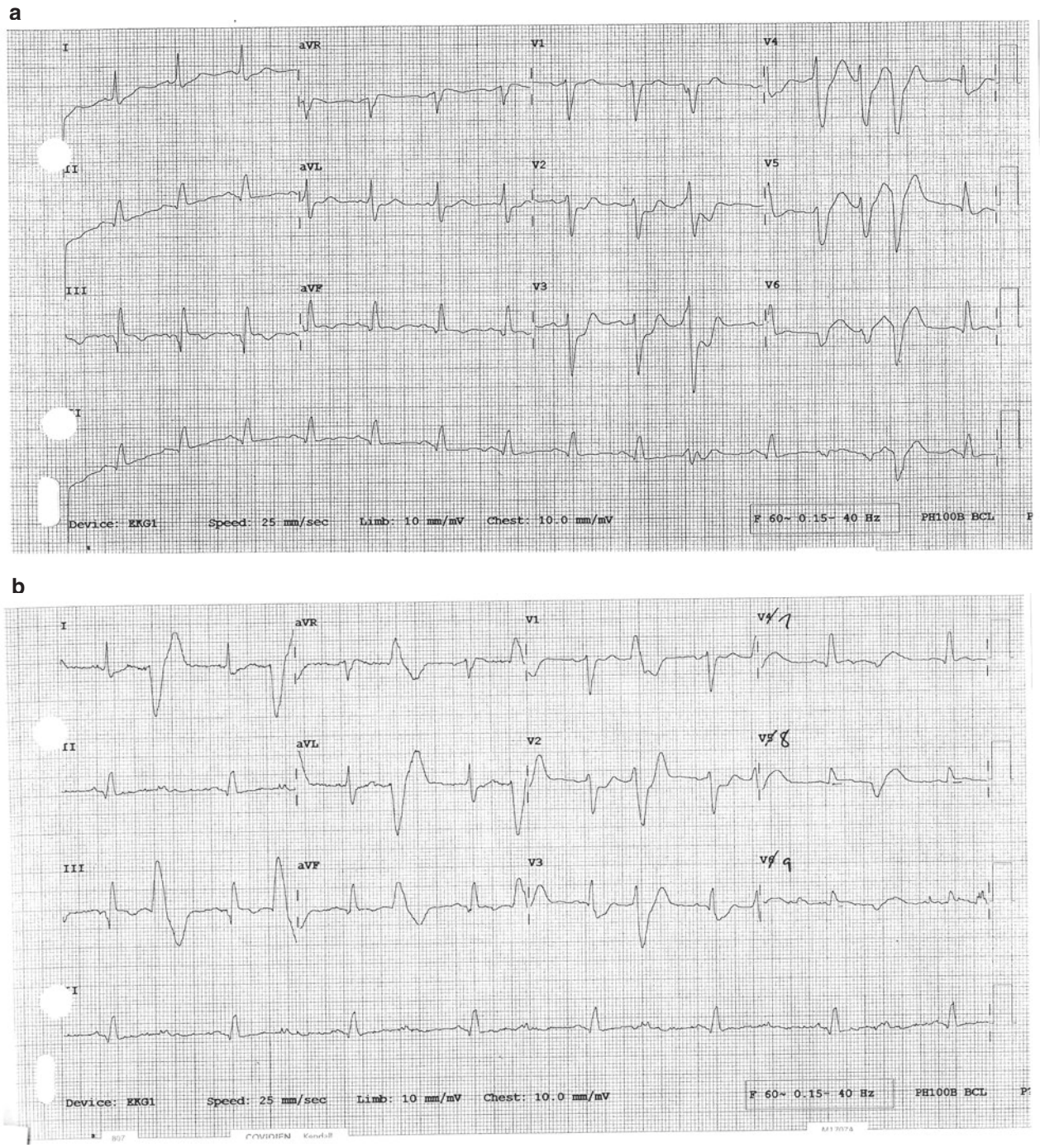


FIGURE 4-1

(**a**) ST depression in leads V2-V3 consistent with posterior wall MI. (**b**) Posterior leads (V7-V9 with ST elevation) consistent with posterior wall MI. Images courtesy of Dr. Philip Podrid, MD. (**c**) Posterior ECG lead placement. (**d**) Right-sided ECG lead placement

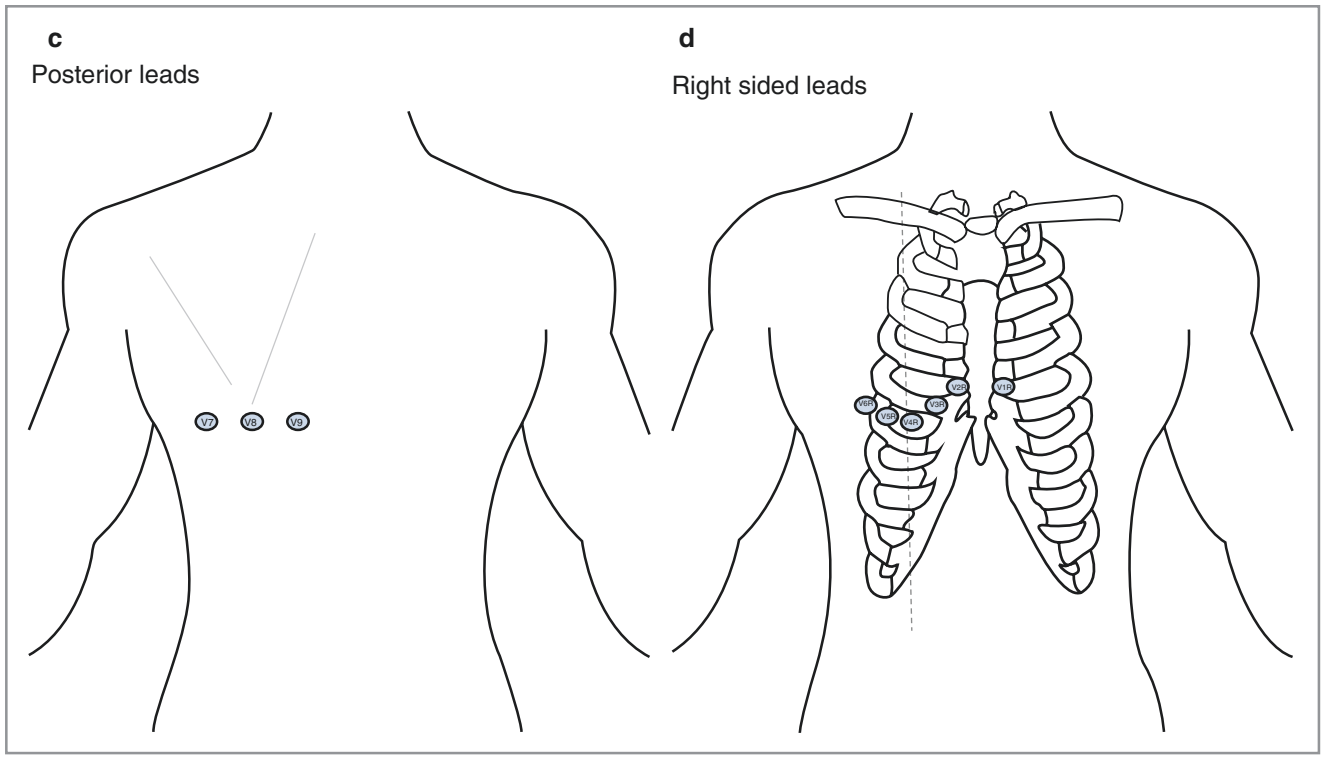


FIGURE 4-1

(continued)

C) **Cardiac Biomarkers**

- Cardiac troponins are the preferred biomarker in an acute ACS [3, 7, 11].
  - Value should be checked on presentation and then repeated.
  - For standard troponin assays, the repeat value can be 3–6 h later.
  - For high sensitivity troponin assays, the repeat value can be 1 h later (or at 3 h if the patient presented very recently, i.e., within 3 h of symptom onset) [7, 12].
- Myocardial injury is defined by at least one elevated cardiac troponin level above the 99th percentile of the upper reference limit of the assay [7].
- Acute myocardial injury is defined by at least one elevated cardiac troponin level and a delta (rise and/or fall) of troponin values. Presence of acute myocardial injury alone does not necessarily mean there is ACS (as injury occurs in myocarditis, acute heart failure, etc.) [7].
- *Acute myocardial infarction is defined as acute myocardial injury with clinical evidence of acute myocardial ischemia* (symptoms of ischemia, new ischemic ECG changes, development of Q-waves, imaging evidence of loss of myocardial viability of wall motion abnormality consistent with ischemia, or coronary thrombus on angiography or autopsy) [7].

RISK STRATIFICATION

A) **Estimating Risk**

- Early risk stratification ensures prompt, appropriate therapy particularly if emergency coronary angiography is not immediately contemplated (e.g. in those with UA/NSTEMI).
- Risk-stratification models such as TIMI (see Table 4-2) or GRACE (Table 4-3) may be helpful in assisting with management strategies [13].
- UA/NSTEMI with increased risk (i.e. TIMI risk score ≥3), particularly those with ST depressions and/or elevated cardiac biomarkers, should be managed with an initial invasive approach (see Initial Conservative vs Invasive Strategy section below) [3, 14].
- BNP (B-type natriuretic peptide) or NT-proBNP (N-terminal pro-B-type natriuretic peptide) can help assess risk in patients with suspected ACS [15].

TABLE 4-2

TIMI RISK SCORE (UA/NSTEMI)

RISK FACTOR (EACH WORTH 1 POINT)
Age ≥ 65 years
≥3 CAD risk factors
Known CAD (stenosis ≥ 50%)
ASA use in past 7 days
≥2 anginal episodes within past 24 h
ST segment deviation ≥0.5 mm
Elevated cardiac biomarkers

ASA aspirin, *CAD* coronary artery disease, *UA* unstable angina [13]

TABLE 4-3

COMPONENTS OF GRACE SCORE

Age
Development (or history) of heart failure
Peripheral vascular disease
Systolic blood pressure
Killip class
Initial serum creatinine
Elevated initial cardiac markers
Cardiac arrest on admission
ST segment deviation

GENERAL ANTI-ISCHEMIC THERAPIES

A) **Oxygen**

- Oxygen only in patients with O2 sat <90%, respiratory distress, or cyanosis [3, 4].

B) **Nitrates**

- Nitrates should be used to treat initial or recurrent angina, improve symptoms of pulmonary congestion, and decrease blood pressure in hypertensive patients [3, 4].
- *Caution in RV MI, severe AS (aortic stenosis), hypovolemia; contraindicated in phosphodiesterase inhibitor use within 24–48 h* [3, 4].

C) **Beta Blockers**

- *Oral beta-blockers are recommended for all ACS unless there are clear contraindications* (e.g. bradycardia, marked first or second degree atrioventricular block, active bronchospasm, signs of HF [heart failure] or low-output state, or increased risk for cardiogenic shock (including SBP [systolic blood pressure] <100 mmHg, HR [heart rate] <60 beats/min or >110 beats/min, age >70 years, delayed presentation, or known severe cardiomyopathy) [3, 4, 16].
- Intravenous beta blockers may be used in hypertensive patients without contraindications.
- Caution in the setting of cocaine toxicity due to potential to provoke coronary spasm.

D) **Calcium Channel Blockers**

- When beta-blockers are contraindicated for non-cardiac reasons, a non-dihydropyridine calcium channel blocker (e.g. diltiazem or verapamil) should be given instead if no contraindications [3, 4, 17, 18].
- Immediate-release dihydropyridine calcium channel blockers (e.g. nifedipine) should not be administered due to the risk of profound hypotension and reflex tachycardia [3, 4, 19].

UNSTABLE ANGINA/NSTEMI (SEE FIG. 4-2)

A) **Initial Angiography Strategy (**Table 4-4)

- The angiography strategy is a major initial branch point, but regardless of the strategy, initial anti-ischemic and antithrombotic therapy should be instituted on presentation, as detailed.
- *Urgent/immediate angiography (i.e., within 2 h) is indicated for patients with refractory angina, recurrent angina/ischemia at rest with low level activity despite intensive medical therapy, heart failure signs/symptoms, new or worsening MR, or hemodynamic or electrical instability* [3, 14].
- Routine angiography strategy: An initial routine angiography strategy involves angiography in all patients, with revascularization as appropriate [3, 14].
  - An early invasive strategy (angiography within 24 h) is indicated for patients at high risk for clinical events (GRACE score >140, elevated or changing cardiac biomarkers, new ST segment depression) [3, 20–22].
  - A delayed invasive strategy (angiography within 72 h) is acceptable in low to intermediate risk patients (diabetes mellitus, LVEF [left ventricular ejection fraction] <0.40, early postinfarction angina, PCI [percutaneous coronary intervention] within 6 months, prior CABG, GRACE score 109–140, TIMI score ≥2, unless there is a clinical change) [3, 20–22].

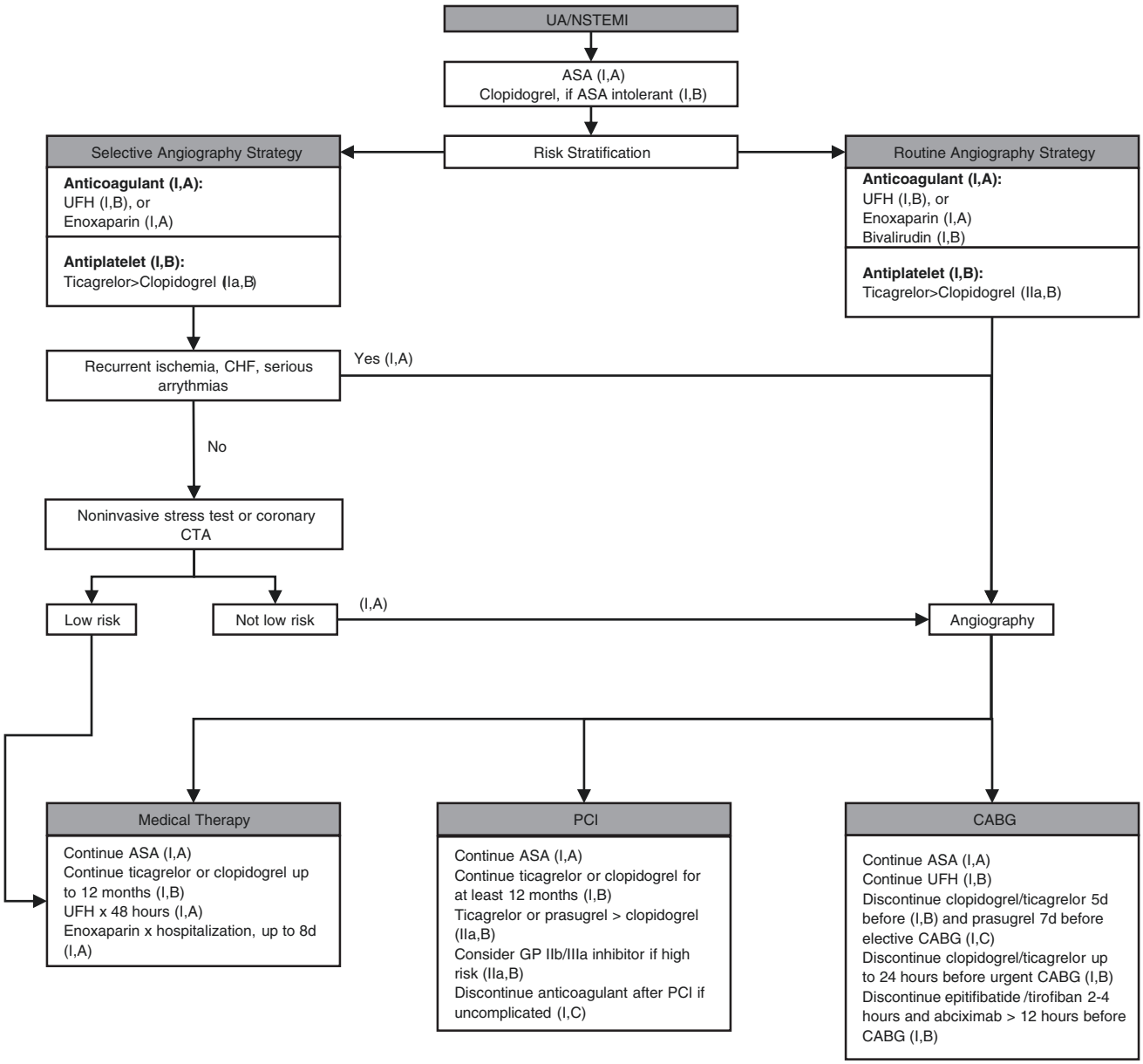


FIGURE 4-2

Algorithm for UA/NSTEMI management. Risk stratification assists in determining the major branchpoint is management strategy. Regardless of strategy, dual antiplatelet therapy in addition to an anticoagulant is recommended. Patients who are initially managed conservatively should undergo further non-invasive testing for additional risk stratification then referred for angiography if indicated and appropriate

- An initial selective angiography strategy involves monitoring the patient, and if they remain symptom-free for 12–24 h, non-invasive stress testing or coronary computed tomographic angiography (CTA) is performed. Invasive coronary angiography is limited to patients with recurrent symptom recurrence or high-risk stress test features. This strategy is acceptable in low risk patients (TIMI 0 or 1, GRACE < 109), low risk troponin negative female patients, or in situations with patient or clinician preference in the absence of high-risk features [3, 14].
- Consider fractional flow reserve (FFR)-guided revascularization when no culprit identified or in non-culprit vessels [23]. However, in patients with multivessel disease in context of MI and cardiogenic shock, culprit-only PCI should be performed [24].

TABLE 4-4

FACTORS ASSOCIATED WITH APPROPRIATE SELECTION OF ROUTINE ANGIOGRAPHY STRATEGY OR SELECTIVE ANGIOGRAPHY STRATEGY IN PATIENTS WITH NSTE-ACS

Immediate invasive (within 2 h)	Refractory angina
	Signs or symptoms of HF or new or worsening mitral regurgitation
	Hemodynamic instability
	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Sustained VT or VF
Early invasive (within 24 h)	None of the above, but GRACE risk score >140
	Temporal change in troponin
	New or presumably new ST depression
Delayed invasive (within 25–72 h)	None of the above but diabetes mellitus
	Renal insufficiency (GFR < 60 mL/min/1.73 m)
	Reduced LV systolic function (EF < 0.40)
	Early post-infarction angina
	PCI within 6 months
	Prior CABG
	GRACE risk score 109–140; TIMI score ≥2
Selective angiography strategy	Low-risk score (e.g., TIMI 0 or 1)
	GRACE risk score <109
	Low-risk Tn-negative female patients
	Patient or clinician preference in the absence of high-risk features

Adapted from Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139–e228 [3]

CABG coronary artery bypass graft, *EF* ejection fraction, *GFR* glomerular filtration rate, *GRACE* Global Registry of Acute Coronary Events, *HF* heart failure, *LV* left ventricular, *NSTE-ACS* non-ST-elevation acute coronary syndrome, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction, *VF* ventricular fibrillation, *VT* ventricular tachycardia

B) Antiplatelet Drugs

■ Aspirin

- ASA (aspirin) reduces MACE (major adverse cardiovascular events) by 46–51% [25].
- Current U.S. guidelines recommend non-enteric-coated 162–325 mg crushed/chewed × 1 then 75–100 mg daily thereafter if medically managed [3, 4, 14].
- In those receiving dual anti-platelet therapy (DAPT) with concurrent P2Y12 receptor blocker, ASA dosing should be 75–100 mg [26].

■ P2Y12 Receptor Blockers

- An agent in this class should be given in addition to ASA regardless of whether the patient is medically managed or undergoes PCI. Given the risk of CABG (coronary artery bypass graft surgery)-related and non-CABG-related bleeding, the decision for P2Y12 receptor blocker administration prior to coronary angiography must be weighed by the likelihood of emergency CABG and risk of bleeding [3, 4, 14, 27].
- *In patients treated with medical management or with PCI, it is reasonable to use ticagrelor over clopidogrel, and in patients treated with PCI, it is reasonable to use prasugrel over clopidogrel for maintenance therapy* [26, 28–30].
- *Although the degree of platelet inhibition is similar between ticagrelor and prasugrel, and randomized controlled trials comparing each to clopidogrel have shown roughly similar magnitudes of benefit, a single head-to-head randomized trial suggests that prasugrel may be superior to ticagrelor in patients for whom inva-*

sive evaluation is planned [31]. *In NSTEMI patients, prasugrel 60 mg should be administered after angiography but before PCI begins with a maintenance dose of 10 mg (5 mg if age ≥ 75 years or weight <60 kg)*

- P2Y12 receptor blocker should be continued for at least 12 months, with longer duration reasonable in patients who are not at high bleeding risk [26, 32, 33].
- In patients receiving CABG and not on anticoagulation, P2Y12 blocker should be resumed after CABG to complete 12 months of therapy [26, 34].
- **Ticagrelor**
  - This agent reversibly inhibits the P2Y12 receptor [3].
  - This agent has a more rapid onset of action and more potent platelet inhibition than clopidogrel and may be considered in cases of clopidogrel resistance.
  - The PLATO trial demonstrated that in ACS patients with or without ST segment elevation, compared with clopidogrel, ticagrelor 180 mg loading dose followed by 90 mg twice daily as soon as possible resulted in a decrease in MACE, including cardiovascular and all-cause mortality [29].
    - There was no increase in overall major bleeding but there was an increase in non-surgical bleeding.
    - When administered with ticagrelor, ASA must be administered at 75–100 mg daily [14, 29].
- **Prasugrel**
  - This agent has a more rapid onset of action with higher levels of platelet inhibition and more reliable inhibition compared to clopidogrel [35].
  - The TRITON-TIMI 38 trial demonstrated that, compared with clopidogrel, prasugrel 60 mg loading and 10 mg daily thereafter resulted in decreased death/MI/stroke in ACS patients with planned PCI. However, there was increased non-surgical, surgical, and fatal bleeding [30].
    - Patients with active bleeding or a history of TIA (transient ischemic attack) or stroke should not receive prasugrel. Additionally, patients ≥75 years old generally should not receive prasugrel except those who are high risk (DM [diabetes mellitus] or prior MI) where the benefit may outweigh the risk of bleeding. Further risk factors for bleeding include body weight <60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (5 mg daily may be considered in patients <60 kg) [26, 30].
  - *Prasugrel should only be administered after angiography as soon as the decision for PCI has been made* [30, 36].
  - In patients with UA/NSTEMI not undergoing revascularization, there was no benefit to treatment with prasugrel over clopidogrel with similar bleeding rates [37].
  - In those undergoing CABG who received prasugrel, this agent should be held for at least 7 days prior to surgery.
  - In one head-to-head trial, prasugrel appeared superior to ticagrelor for reducing the composited endpoint of death, MI, or stroke at 1 year, without an increased bleeding risk [31].
- **Clopidogrel**
  - Loading with 300 mg, then administering 75 mg daily along with ASA results in a 20% reduction in MACE by 9 months, with effects as early as 24 h, compared to aspirin alone [3, 4, 27, 38].
  - Compared to a 300 mg loading dose, a 600 mg loading dose achieves faster antiplatelet activity within 2–3 h and is recommended if angiography and revascularization is planned that day.

- In CURRENT-OASIS 7, double-dose clopidogrel (600 mg load, 150 mg daily × 7 days, then 75 mg daily) compared to standard dosing in those undergoing PCI resulted in a decrease in stent thrombosis [39].

■ In patients undergoing CABG, clopidogrel should be held for at least 5 days prior to surgery [3].
■ Although 20–25% of patients are resistant to standard clopidogrel doses, optimal clopidogrel dosing based on individual genotyping and platelet reactivity testing has not yet been established, although studies show poorer outcomes in those with clopidogrel resistance.

- **Cangrelor**

■ Intravenous infusion of P2Y12 receptor blocker that has an almost immediate antiplatelet effect and possesses a very short half-life (~3 min).
■ Compared with clopidogrel or placebo, cangrelor reduces PCI periprocedural thrombotic complications, but leads to increased bleeding [40].
■ Indicated as an adjunct to PCI in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor

■ **GP IIb/IIIa (Glycoprotein IIb/IIIa) Inhibitors**

- These intravenous agents block the final common pathway for platelet aggregation.
- Most patients do not require GP IIb/IIIa inhibitors. They can be given in ACS patients treated with dual antiplatelet therapy undergoing a routine angiography strategy who demonstrate high-risk features [3, 14, 41]. They can also be administered to patients undergoing PCI who have not been adequately treated with upstream dual antiplatelet therapy.
- GP IIb/IIIa inhibitors can be considered upstream of coronary angiography but the clinical benefit compared with provisional use at the time of PCI is unclear and comes at the expense of more bleeding [42–45]. Heparin should be co-administered with GP IIb/IIIa inhibitors [14]. Contemporary access-site bleeding rates have been reduced by the growing use of radial access.
- Typically, these agents are not administered if a patient is conservatively managed unless there is recurrent ischemia.

C) **Anticoagulants**

■ **UFH (Unfractionated Heparin)**

- UFH should be administered with antiplatelet therapy as a bolus followed by a continuous infusion [3, 14].
- When medically managed, patients should receive UFH for 48 h.
- *After a successful uncomplicated PCI, UFH should be discontinued unless there are other indications for anticoagulation.*
- In those with clear heparin-induced thrombocytopenia, an alternative nonheparin anticoagulant (e.g. bivalirudin, argatroban, fondaparinux, lepirudin) should be used.

■ **Enoxaparin**

- Compared to UFH, enoxaparin results in a 10% reduction in subsequent death or MI, but the benefit is largely seen in patients undergoing an initial conservative approach with increased bleeding in patients undergoing an invasive strategy [46–49].
- For medically managed patients, enoxaparin 1 mg/kg SC (subcutaneous) every 12 h should be continued for the duration of the hospitalization, up to 8 days [3].

- For patients undergoing PCI who have received fewer than two therapeutic SC doses or received the last SC dose 8–12 h prior to PCI, an additional 0.3 mg/kg IV (intravenous) dose should be administered at the time of PCI [3].
- The dose of enoxaparin should be reduced in those with impaired renal function, or unfractionated heparin should be considered [3].

■ **Bivalirudin**

- In invasively managed patients, bivalirudin-based regimens compared to heparin-based regimens may lead to higher rates of myocardial infarction and stent thrombosis but cause less bleeding when compared to heparin combined with a GP IIb/IIIa inhibitor [50, 51]. Bivalirudin does not lead to lower rates of myocardial infarction, death, and major bleeding if compared to use of heparin alone [52, 53].

D) **Fibrinolytics**

■ *There is no benefit for fibrinolysis in UA/NSTEMI and is not recommended* [3, 54, 55]. In patients with ST segment depression in leads V1-V2, it is important to exclude a posterior STEMI, which is an indication for fibrinolysis.

STEMI (SEE FIG. 4-3)

A) **Reperfusion**

■ The primary management goal of STEMI is restoration of coronary blood flow [4, 14, 56].

■ **Primary PCI** *(see Chap. 9)*

- Improves survival compared to fibrinolysis.
- For patients presenting within 12 h of symptom-onset, PCI should be within 90 min of first medical contact in a hospital with PCI capabilities, and up to 120 min in hospitals without PCI capabilities; for those presenting very early (within 3 h), an even earlier door-to-balloon time is recommended [4, 14, 56].
- For those presenting 12–24 h after symptom-onset, primary PCI should be considered if there is severe HF, hemodynamically-significant VT (ventricular tachycardia), or persistent ischemic symptoms [4, 14, 56].
- Given the results of the SHOCK trial, patients that develop shock within 36 h of an MI who can be revascularized within 18 h of shock, should undergo revascularization [57].
- In patients with STEMI and multivessel coronary disease without hemodynamic compromise, PCI of non-culprit lesions either during or after the index hospitalization reduces risk of cardiovascular death or myocardial infarction [58]. However, in patients with multivessel disease in context of MI and cardiogenic shock, culprit-only PCI should be performed [24].

■ **Fibrinolysis**

- If primary PCI is not available within 120 min, then fibrinolytic therapy should be administered with the door-to-needle time ≤30 min [4].
- Survival benefit is greatest when fibrinolytics are administered within the first 3 h of symptom-onset but patients presenting within the first 12 h are eligible [59, 60].
- Late therapy (12–24 h) can be considered in patients with ongoing ischemia, particularly in those with large anterior MI [4].
- Absolute contraindications: any prior intracranial hemorrhage, severe uncontrolled hypertension unresponsive to therapy, active bleeding or bleeding diathesis, suspected aortic dissection, known structural cerebrovascular lesion (e.g. arteriovenous malformation), known malignant intracranial neoplasm, and ischemic stroke within the past 3 months, intracranial or intraspinal surgery within past 2 months [4].

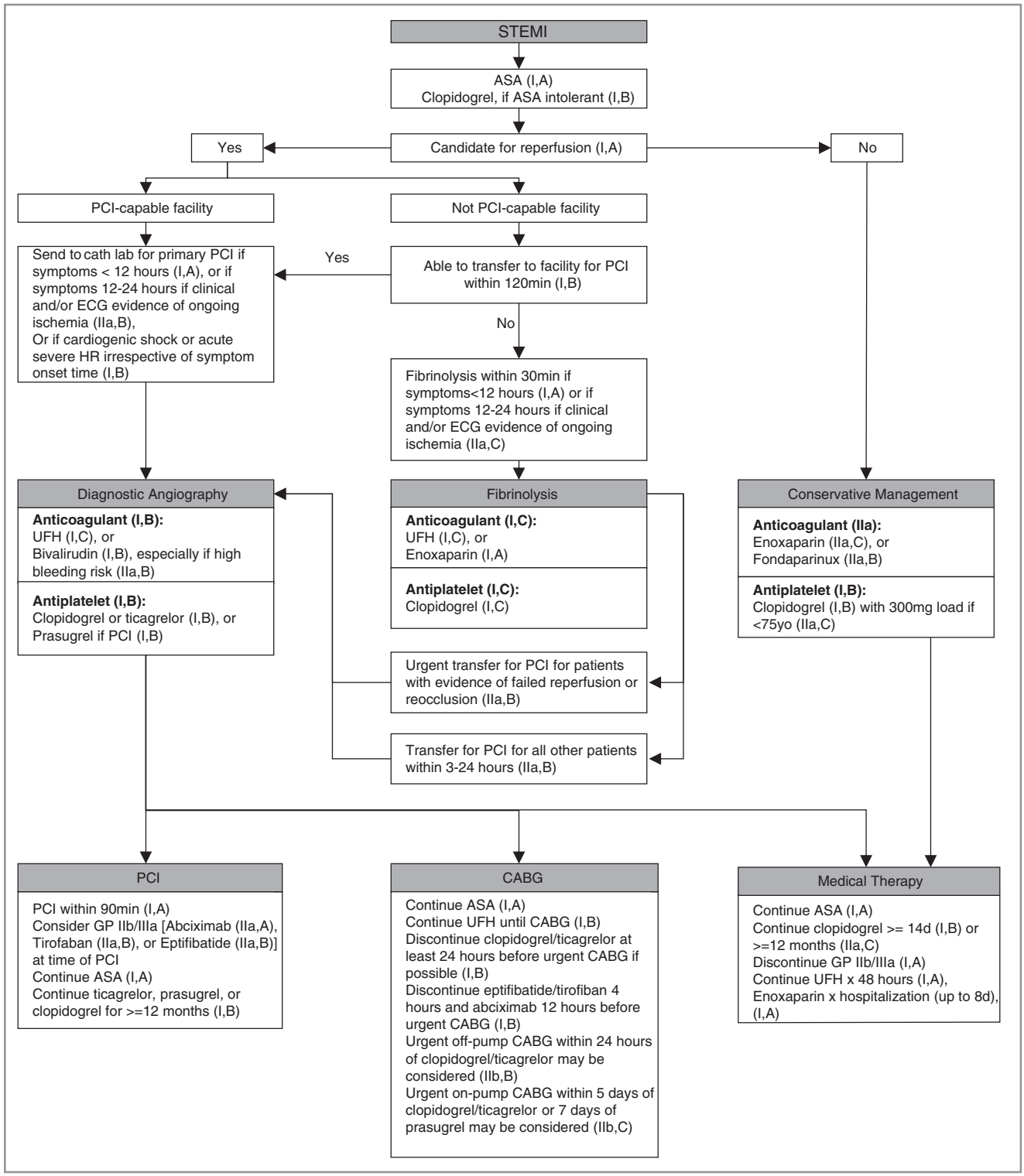


FIGURE 4-3

Algorithm for STEMI management. Reperfusion therapy is critical in STEMI management, and if PCI is available, it is the preferred modality for the restoration for coronary blood flow. Dual antiplatelet therapy in addition to an anticoagulant is recommended

- Relative contraindications: significant hypertension (≥180/110 mmHg), ischemic stroke more than 3 months previously, dementia, any known intracranial disease that is not an absolute contraindication, traumatic or prolonged (>10 min) CPR (cardiopulmonary resuscitation), major surgery within the preceding 3 weeks, internal bleeding within the preceding 2–4 weeks or an active peptic ulcer, non-compressible vascular punctures, pregnancy, current anticoagulant therapy, prior exposure or allergic reaction (for streptokinase or anistreplase) [4].
- Routine, or transfer for, coronary angiography 3–24 h after fibrinolysis is reasonable even in hemodynamically stable STEMI patients with evidence of successful reperfusion [4, 14, 61].

■ **Rescue PCI**

- Rescue PCI should be performed in patients who, despite fibrinolytic therapy, manifest severe mechanical (i.e. CHF or cardiogenic shock) or electrical (i.e. hemodynamically-significant VT) complications [4, 14, 62]. Rescue PCI should be considered for patients with evidence for unsuccessful fibrinolysis (i.e. <50% ST segment resolution within 90 min of fibrinolysis therapy) with a moderate to large area of myocardium at risk [4, 14].

■ **CABG**

- Indications include failed PCI with persistent pain or hemodynamic instability, persistent ischemia refractory to medical therapy with suitable anatomy but not candidates for PCI or fibrinolysis with a significant area of myocardium at risk, at the time of post-infarction VSR (ventricular septal rupture), free wall rupture, MR due to papillary muscle rupture, or cardiogenic shock with left main and/or severe multivessel disease [4].

B) **Antiplatelet Drugs**

■ **Aspirin**

- Current U.S. guidelines recommend 162–325 mg crushed/chewed × 1 then 75–100 mg daily thereafter if medically managed [4].

■ **P2Y12 Receptor Antagonists**

- An agent from this class should be added to ASA for STEMI patients.
- In patients undergoing PCI for STEMI, clopidogrel, prasugrel, or ticagrelor are options with dosing and duration similar to those undergoing PCI in UA/NSTEMI [29, 30, 63].
- *Although the degree of platelet inhibition is similar between ticagrelor and prasugrel, and randomized controlled trials comparing each to clopidogrel have shown roughly similar magnitudes of benefit, a single head-to-head randomized trial suggests that prasugrel may be superior to ticagrelor in patients for whom invasive evaluation is planned* [31]. In STEMI patients, prasugrel 60 mg should be loaded prior to angiography, with a maintenance dose of 10 mg (5 mg if age ≥ 75 years or weight < 60 kg)
- *In patients undergoing fibrinolysis, the only P2Y12 receptor blocker that has been studied and shown to be safe is clopidogrel* 75 mg daily with 300 mg (not 600 mg) loading dose, which can be administered in those <75 years old; a maintenance dose of 75 mg daily should be continued for a minimum of 14 days and ideally 12 months [26, 44, 45, 64, 65].

■ **Glycoprotein IIb/IIIa Inhibitors**

- In the era of dual antiplatelet therapy, the additional benefit of GP IIb/IIIa inhibition is uncertain but may be considered in those with a large or persistent thrombus burden and/or not adequately preloaded with an P2Y12 receptor antagonist [4, 14].

C) **Anticoagulants**

- **Unfractionated Heparin**
  - UFH should be given to those receiving PCI or fibrin-specific fibrinolytics (e.g. tissue plasminogen activator, reteplase, and tenecteplase) [4, 14].
  - UFH should be given to those receiving non-selective fibrinolytic agents (e.g. streptokinase) at high risk for systemic emboli (e.g. anterior STEMI) [4].
  - In those who are medically managed or given fibrinolytics, UFH is only recommended for 48 h given the limited evidence for prolonged infusions and increased risk for bleeding and thrombocytopenia unless there is another indication for ongoing anticoagulation.
- **Bivalirudin**
  - In invasively-managed patients, bivalirudin-based regimens compared to heparin-based regimens may lead to higher rates of myocardial infarction and stent thrombosis, but less bleeding compared to heparin combined with a GP IIb/IIIa inhibitor [50, 51]. Bivalirudin does not lead to lower rates of MI, death, and major bleeding if compared to use of heparin alone [52, 53].
- **Enoxaparin**
  - In patients who receive fibrinolytics, data suggests a benefit of enoxaparin over UFH in reducing ischemic endpoints but increase in bleeding [66, 67].
  - For those who received fibrinolytics, enoxaparin may be substituted for UFH for the duration of the hospitalization, up to 8 days.

ADJUNCTIVE THERAPIES

A) **ACE (Angiotensin Converting Enzyme) Inhibitors/ARBs (Angiotensin II Receptor Blockers)**

- Early studies demonstrated a benefit of early ACE inhibitor administration particularly in those with an anterior MI. ACE inhibition in systolic dysfunction and CHF have a more substantial mortality benefit (20–30%) [68–70].
- *An oral ACE inhibitor is recommended within the first 24 h in those with an anterior STEMI and/or LVEF < 40% or HF, and in those with hypertension, diabetes mellitus, or stable CKD (chronic kidney disease) in the absence of hypotension, AKI (acute kidney injury), hyperkalemia, allergy, or bilateral renal artery stenosis* [3, 4].
- ARBs are appropriate alternatives to ACE inhibitors for patients who may not be to tolerate ACE inhibitors.

B) **Aldosterone Inhibitors**

- *In patients with a recent MI and an LVEF ≤ 40% with CHF and/or DM on beta-blockers and ACE inhibitors, treatment with eplerenone reduces mortality* [71].

C) **Lipid Management**

- It is reasonable to check fasting lipid panel within 24 h of presentation [3, 4].
- High intensity statin therapy should be started in all patients with ACS without contraindications [3, 4, 72, 73].
- *In patients post-ACS on statin therapy with LDL-C (Low density lipoprotein cholesterol) 50–100 mg/dL, adding ezetimibe lowers MACE* [74].
- In patients with CAD including those with ACS at least 4 weeks prior, adding PCSK9 (proprotein convertase subtilisin kexin 9) inhibitor reduces MACE [75, 76].
- Non-statin therapies should be added to a statin in patients with LDL > 70 unless age > 75 and not very high risk, with some advocating for lower thresholds [77–79].

D) **ICD (Implantable Cardioverter Defibrillator) Placement**

- Patients who develop sustained VT or VF (ventricular fibrillation) >48 h after STEMI that is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities should have ICD placement before discharge [4].
- Patients with a reduced ejection fraction after MI who do not meet criteria for immediate ICD placement should have an assessment of ejection fraction and HF symptoms after at least 40 days after MI or 90 days post-revascularization to evaluate whether ICD therapy is indicated [4, 80–82].

E) **Diet & Lifestyle Counseling**

- Smoking cessation counseling in the hospital is recommended [3, 4].
- Diet, exercise, and stress management counseling may be beneficial [3, 4].
- Comprehensive cardiovascular rehabilitation referral is recommended [3, 4].
- Influenza and pneumococcal vaccination is recommended [3, 4].

REVIEW QUESTIONS

1. A 72 year-old woman presents to the emergency department with recurrent dyspnea and progressive epigastric discomfort with minimal exertion over the preceding week with one more severe such episode in the last 24 h. Past medical history is notable for hypertension and hyperlipidemia. Her medications include hydrochlorothiazide 25 mg daily, nifedipine sustained-release 60 mg daily, and pravastatin 40 mg daily. Her father had a myocardial infarction leading to CABG at the age of 73 years old. Upon physical exam, her temperature is 37.6 °C, blood pressure 110/72 mmHg, heart rate 98 bpm, respiratory rate 14/min, O2 saturation 100% on room air. She is in no acute distress. Her jugular venous pressure is 5 cm H_2O. Lungs are clear to auscultation bilaterally and her heart sounds are regular with a normal S1 and S2 without extra heart sounds. Complete blood count, liver function tests, electrolytes, coagulation tests are normal, and her serum creatinine is 1.22 mg/dL. ECG shows normal sinus rhythm and no notable abnormalities. Initial high sensitivity troponin is elevated at 65 ng/L with 1 h repeat value at 30 ng/L (99% URL for assay is 14).

Which of the following is the next appropriate step in management?

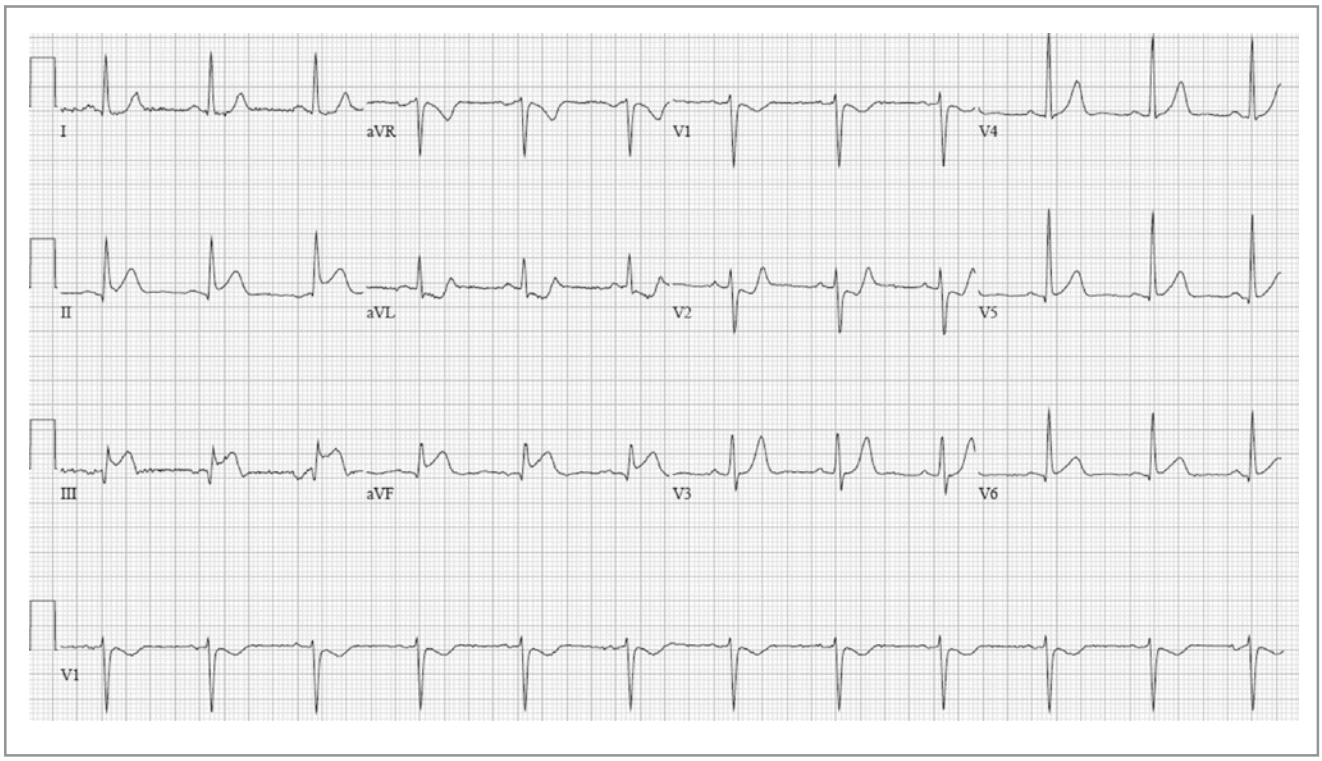
A. Search for non-ischemic causes of acute myocardial injury since this is unlikely acute MI.
B. Administer ASA 325 mg and search for non-ischemic causes of myocardial injury since this is unlikely acute MI.
C. Administer ASA 325 mg, ticagrelor 180, metoprolol, and UFH IV (intravenous) and plan for further risk stratification with non-invasive stress testing.
D. Administer ASA 325 mg, ticagrelor 180, metoprolol, and UFH IV and plan for coronary angiography in the next 24 h.
E. Administer ASA 325 mg, ticagrelor 180, metoprolol, and UFH IV and proceed emergently to coronary angiography.

2. A 42 year-old healthy man who smokes cigarettes with no significant past medical history presents to the emergency department who complains of recurrent 15–20 min episodes of substernal chest pain radiating to his left arm with diaphoresis at rest on the day of presentation. Over the past 3 days, he acknowledges similar symptoms that occur with exertion and are relieved by rest. His last episode of chest pain was in the ambulance coming to the emergency department and was relieved with one tablet of sublingual nitroglycerin and aspirin 325 mg chewed. On examination, his temperature is 37.2 °C, blood pressure 132/82 mmHg, heart rate 72 bpm, respiratory rate 14/min, O2 saturation 100% on room air. He is resting comfortably without jugular venous pressure elevation and with normal cardiac and pulmonary examinations. Complete blood count, liver function tests, electrolytes, renal function, coagulation tests are normal and troponin T is elevatevd at 0.50 ng/mL. ECG shows normal sinus rhythm with 1.0 mm ST depressions in II/III/aVF. IV Heparin bolus followed by infusion is initiated.

In addition to oral beta-blockers, what is the best next agent to administer?

A. Reteplase.
B. Fondaparinux.
C. Clopidogrel.
D. Ticagrelor.
E. Eptifibatide.

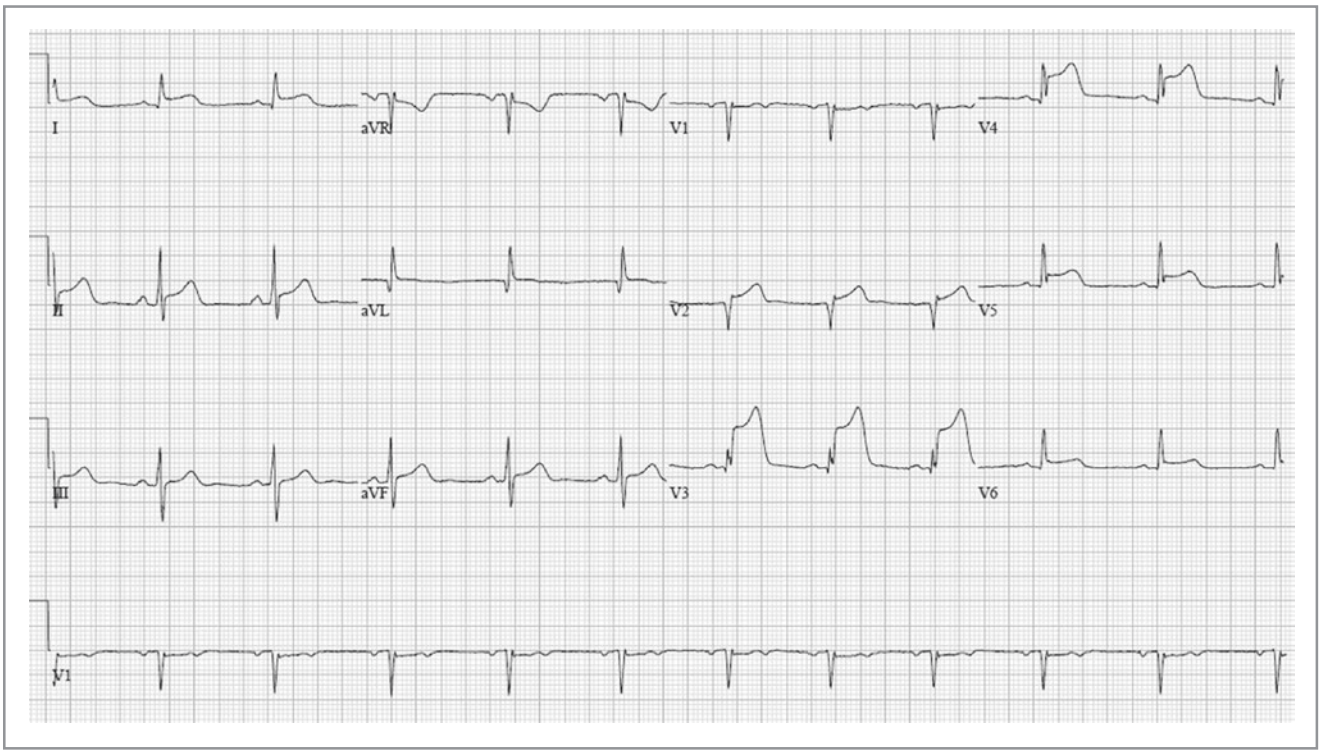
3. A 36 year-old woman who is 36 weeks pregnant presents to the emergency department with chest pain. Her pregnancy thus far has only been complicated by gestational diabetes which she has been able to manage with diet. She reports just over 3 h of substernal chest pain without radiation but with associate dyspnea. Past medical history and family history are unremarkable. She is only taking a prenatal vitamin. Upon triage, her temperature is 37°C, heart rate 92 bpm, blood pressure 152/90 mmHg (on both arms), respiratory rate 16/min, O2 saturation 100% on room air. Her chest discomfort has improved with nitroglycerin sublingual but it persists and she appears uncomfortable. Jugular venous pressure does not appear elevated and she has normal cardiac and lung sounds. Her triage ECG is shown below.



Which of the following is correct regarding the next steps in management?

A. She should be promptly taken to the cardiac catheterization with a planned 90 min door-to-balloon time.
B. Alteplase should be immediately administered.
C. An initial conservative approach without initial PCI or fibrinolysis is preferred.
D. Aspirin should not be administered.
E. The baby should be emergently delivered then the patient should immediately be taken to cardiac catheterization.

4. A 50 year-old man presents to the emergency department with chest pain. While having an emotional argument with his wife, he suddenly developed left-sided substernal chest pain that radiated to his left jaw with associated diaphoresis and shortness of breath. He took aspirin 325 mg at home and called emergency medical services. Upon arrival of emergency services, the patient's pain improved with two tablets of sublingual nitroglycerin but mild discomfort and dyspnea persisted. His past medical history is notable for hyperlipidemia, for which he takes atorvastatin 40 mg. Upon arrival to the emergency department, his temperature is 37.6 °C, heart rate 92 bpm, blood pressure 174/98 mmHg (similar in both arms), respiratory rate 20/min, and oxygen saturation 98% on room air. He appears uncomfortable. Jugular venous pressure is estimated at 6 cm H_2O. Lung fields are clear to auscultation bilaterally. Cardiac exam reveals regular rate and rhythm, normal S1 and S2, and no extra heart sounds. Extremities reveal good distal pulses and are warm without peripheral edema. ECG is shown below. He was promptly taken to the cardiac catheterization lab where he was found to have a 99% mid-LAD lesion with TIMI-2 flow without other significant coronary artery disease. Prasugrel 60 mg was administered and an everolimus-eluting stent was successfully placed. He was discharged on atorvastatin 80 mg, in addition to aspirin 81 mg, prasugrel 10 mg, metoprolol XL 50 mg, and lisinopril 10 mg. A repeat lipid panel in outpatient cardiology clinic 6 weeks post-MI revealed and LDL-C of 80 mg/dL, High density lipoprotein cholesterol of 48 mg/dL, and Triglycerides of 189 mg/dL.



Which of the following is the best regimen for lipid management?

A. Continue atorvastatin 80.
B. Continue atorvastatin 80 and start ezetimibe 10.
C. Continue atorvastatin 80 and start fenofibrate 130.
D. Stop atorvastatin and start evolocumab.

REVIEW QUESTION ANSWERS

1. **Answer**: **D**. In this case, a woman with coronary artery disease risk factors presents with an acute NSTEMI. She has acute myocardial injury as evidenced by elevated troponin level above the 99% URL and a delta in troponin value of >20% on repeat measurement. Given features of the history consistent with ischemic symptoms in conjunction with acute myocardial injury, this is acute myocardial infarction per the Fourth Universal Definition of MI. She does not have ECG features consistent with STEMI. She should receive appropriate medical management for acute NSTEMI with aspirin, ticagrelor, beta blocker, and anticoagulant. She would not be an appropriate candidate for a selective angiography strategy given her elevated troponins, TIMI score of 2, and her GRACE score of 127. Invasive coronary angiography should be pursued within the next 72 h, and ideally within the next 24 h given her elevated troponin. She does not exhibit any signs/symptoms of heart failure, acute mitral regurgitation, or any hemodynamic or electrical instability so does not meet criteria for emergent catheterization lab activation.

2. **Answer**: **D**. This scenario depicts a gentleman who presents with an NSTEMI with frequent recurrent angina but currently without ongoing ischemic symptoms. Given his TIMI risk score of UA/NSTEMI is 3, his troponin elevation, and ECG changes, and he is in a high-risk category. Thus, the data supports an early invasive strategy, ideally within the first 24 h for high risk individuals according to the TIMACS trial. Fibrinolysis is not recommended for the management of NSTEMI. Since he will likely proceed to coronary angiography soon, fondaparinux would not be the best choice given the risk of catheter thrombosis and angiography/PCI should not proceed without the co-administration of UFH. While clopidogrel could be administered, ticagrelor is a better option given the results of the PLATO trial which showed that, compared with clopidogrel, 180 mg loading followed by 90 mg twice daily as soon as possible resulted in a decrease in MACE. Compared to ticagrelor, a GP IIb/IIIa inhibitor would not be appropriate in this setting unless there was a high chance of needing urgent/emergent cardiac surgery that would be delayed by oral DAPT administration.

3. **Answer**: **A**. Risk factors for MI in pregnancy include age (>30 yo), obesity, diabetes mellitus, hypertension, smoking, antiphospholipid antibody syndrome. The most common etiologies include underlying coronary atherosclerosis and associated thrombosis and spontaneous coronary artery dissection (SCAD). SCAD is most common in the third trimester and within the first 1–2 months post-partum secondary to progesterone-mediated endothelial changes, increased eosinophil proteases, and diminished prostacyclin expression. The initial management of choice for STEMI in pregnancy is still emergent coronary angiography, with PCI if there is TIMI 0-1 flow. Given the relatively high rate of coronary artery dissection, coronary angiography should be performed very cautiously. Fibrinolytics are relatively contrain-

dicated in pregnancy, particularly if labor and delivery are imminent or have happened recently. If possible, an initial conservative approach is preferred for NSTEMI with non-invasive evaluation but reperfusion therapy, similar to non-pregnant patients, is critical for STEMI management. Low doses (81–162 mg of aspirin, particularly in the second and third trimester have been found to be safe and antiplatelet therapy is important in the management of ACS in these patients. The patient would likely not tolerate the added physiologic stress of child birth in the setting of a STEMI and emergent delivery is not indicated for the purposes of managing her STEMI.

4. **Answer: B**. This is a gentleman with history of hyperlipidemia who presents with a STEMI. His LDL-C is not adequately controlled despite a high potency statin. While his LDL-C is below traditional historical targets for someone without diabetes, results of the IMPROVE-IT and ODYSSEY trials suggest that patients he would benefit from the addition of a non-statin therapy to lower his LDL-C even further. In the IMPROVE-IT trial, the addition of ezetimibe to simvastatin reduced MACE and should be started in this case. Fibrates such as fenofibrate should not be added as a non-statin therapy in the absence of hypertriglyceridemia since there is no clear evidence of benefit in this setting with currently available drugs on the market. A PCSK9 inhibitor such as evolocumab is an alternative non-statin therapy to lower LDL-C, though this should be added to rather than replacing his atorvastatin, per the FOURIER trial.

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CHAPTER 5

ROMIT BHATTACHARYA AND PRADEEP NATARAJAN

Primary Prevention of Coronary Artery Disease

CHAPTER OUTLINE

ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ACTH	Adrenocorticotropic hormone
ADA	American Diabetes Association
AHA	American Heart Association
AKI	Acute kidney injury
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARA	Aldosterone receptor antagonists
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
ATP III	Adult Treatment Panel III
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blocker
CE	Cholesterol esters
CETP	Cholesterol ester transfer protein
CHD	Coronary Heart Disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
CM	Chylomicron
CPAP	Continuous positive airway pressure
CT	Computed tomography
CVD	Cardiovascular Disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DM1	Type 1 diabetes mellitus
DM2	Type 2 diabetes mellitus
DPP	Diabetes Prevention Program
DPP4	Dipeptidyl protease-4
DPS	Diabetes Prevention Study

DSMB	Data Safety and Monitoring Board
eGFR	Estimated glomerular filtration rate
EKG	Electrocardiogram
FC	Free cholesterol
FDB	Familial defective apolipoprotein B
FFA	Free fatty acids
FH	Familial hypercholesterolemia
GDMT	Guideline-directed management and therapy
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
HbA1c	Glycosylated hemoglobin
HDL-C	High density lipoprotein cholesterol
HF	Heart Failure
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
HMG-CoA	Hydroxymethylglutaryl-Coenzyme A Reductase
HYVET	Hypertension in the Very Elderly Trial
IDL	Intermediate density lipoprotein
ISH	Isolated systolic hypertension
IV	Intravenous
JNC 7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LCAT	Lecithin cholesterolacyl transferase
LDL-C	Low density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein lipase
LV	Left ventricle
LVH	Left ventricular hypertrophy
LVSD	Left ventricular systolic dysfunction
MI	Myocardial Infarction
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHLBI	The National Heart, Lung, and Blood Institute
NSAIDs	Non-steroidal anti-inflammatory drugs
OSA	Obstructive sleep apnea
PA	Primary aldosteronism
PAC	Plasma aldosterone concentration
PAD	Peripheral arterial disease
PCSK9	Proprotein convertase subtilsin-kexin type 9
PL	Phospholipids
PPAR	Peroxisome proliferator-activated receptor
PRA	Plasma renin activity
RAAS	Renin angiotensin aldosterone system
RAS	Renal artery stenosis
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SGLT-2	Sodium-glucose transport protein 2
SHEP	Systolic Hypertension in the Elderly Program
SLE	Systemic lupus erythematosis
SPRINT	Systolic Blood Pressure Intervention Trial
TG	Triglycerides
VLDL	Very low density lipoproteins

INTRODUCTION

Cardiovascular Disease (CVD) causes about 17 million deaths annually, and is the leading cause of death in the U.S. and worldwide, accounting for over 30% of all deaths globally. Diagnosis and delineation of effective non-pharmacological and pharmacological interventions are key to the prevention of cardiovascular diseases ('primary prevention') and of the risk factors themselves ('primordial prevention'). To that end, we focus on four entities in the following chapter: Lifestyle Recommendations, Hypertension, Diabetes, and Lipoprotein Disorders [1].

CARDIOVASCULAR RISK AND LIFESTYLE

In 2019 the American College of Cardiology (ACC) and the American Heart Association (AHA) jointly released a clinical practice Guideline on the Primary Prevention of Cardiovascular Disease [2]. The guideline stresses healthy lifestyle choices throughout life, shared decision making with patients and providers, assessment tools to stratify lifetime risk, and management of common conditions affecting risk of atherosclerotic cardiovascular disease (ASCVD)—including nutrition, obesity, hypertension, diabetes, dyslipidemia, tobacco use and aspirin use.

Cardiovascular Risk

All approaches to prevent ASCVD, heart failure, and atrial fibrillation should include promotion of a healthy lifestyle throughout life. Understanding both social determinants of health and medical comorbidities are key elements of risk assessment, which may also be addressed through non-pharmacological means.

Social Determinants of Health and Primordial Prevention

The guidelines identify that socioeconomic factors are strong predictors of cardiovascular disease (CVD) and health worldwide and that the five main domains of non–health-related measures that affect health outcomes should be considered, including:

- Housing instability
- Food insecurity
- Transportation difficulties
- Utility assistance needs
- Interpersonal safety

These factors begin to affect CVD risk from early in life and continue to affect access to care and adherence to therapy. Failure to address the impact of social determinants of health impedes efficacy of proven prevention recommendations. Since these risks are not incorporated into current risk calculators, they must be separately considered by providers [2].

Assessing Risk of Cardiovascular Disease

Assessment of CVD risk is the foundation of primary prevention—a starting point for patient-provider discussions, as well as initiation of therapies as noted in the sections to follow. The risk estimates are based on the ASCVD Risk Score (ACC/AHA Pooled Cohort Equations CVD risk calculator, available at *http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/*) first introduced alongside the 2013 cholesterol clinical practice guidelines. The risk calculator integrates information about multiple CVD risk factors to generate an estimated 10-year risk of developing ASCVD. The Pooled Cohort Equation (PCE) however, is best validated in non-Hispanic black and white populations and has been **shown to overestimate and underestimate risk in certain subgroups** [2].

- The PCE may *underestimate* risk in individuals with chronic inflammatory conditions (e.g., autoimmune disease, HIV infection) or socioeconomic disadvantage not captured in current risk-scoring models.
- The PCE may *overestimate risk* in those with higher socioeconomic position and continual access to care and preventive services, which could lead to overtreatment of those less likely to derive clinical benefit from pharmacotherapies.
- The PCE *poorly discriminates* risk at age extremes (<40 years and >70 years) since age is the dominant factor in 10-year ASCVD prediction.

Intermediate or Borderline Risk:

- In individuals with ***intermediate risk* (7.5–19.9% by the PCE**) or select individuals with *borderline risk* (5% to <7.5% risk by PCE), statin prescriptions are appropriate.
- If there is uncertainty about statin prescriptions, **risk-enhancing factors** may also be used to identify individuals at higher risk and guide therapeutic decisions (discussed in the section on Lipoprotein Disorders) (See Table 5-1)
- If uncertainty persists, **coronary artery calcium (CAC) scores** can be used to refine risk (discussed in the section on Lipoprotein Disorders)
  - A CAC score of 0 Agatston units (AU) is associated with a low 5–10% absolute risk of ASCVD events in epidemiologic studies, and could be used as the basis to defer statins.
  - A CAC score of >0, especially >100 AU, strengthens the recommendation for statin prescriptions.

Very High-Risk ASCVD:

- A cohort of patients already with ASCVD but at increased risk for recurrent events is newly defined, which includes patients who have had an acute coronary syndrome (ACS) within the last 12 months, multiple myocardial infarctions (MI), and those with multiple risk factors (strokes, peripheral arterial disease, diabetes) who are discussed in more depth in the section on lipid management.

TABLE 5-1

RISK-ENHANCING FACTORS

RISK-ENHANCING FACTORS

- **Family history of premature ASCVD** (males, age < 55 years; females, age < 65 years)
- **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL; non–HDL-C 190–219 mg/dL
- **Metabolic syndrome** (three of the following: increased waist circumference, elevated triglycerides [>150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women])
- **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions**, such as psoriasis, RA, lupus, or HIV/AIDS
- **History of premature menopause** (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia
- **High-risk race/ethnicity** (e.g., South Asian ancestry)
- **Lipids/biomarkers**: associated with increased ASCVD risk

– Persistently elevated triglycerides (≥175 mg/dL, nonfasting)
– If measured:

Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
Elevated apoB (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C > 160 mg/dL and constitutes a risk-enhancing factor
ABI (<0.9)

[a]Adapted from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Frequency of Risk Assessment

- For adults 40–75 years of age, clinicians should *routinely assess* 10-year ASCVD risk
- For adults 20–39 years of age, it is reasonable to assess traditional ASCVD risk factors *every 4–6 years*.

Principles of Risk Reduction

Shared Decision Making

- Team-based care with multidisciplinary health professionals, patients and family members have been shown to result in greater ASCVD risk reduction.
- Collaborative decision-making is more likely to address potential barriers to treatment options than guidance offered without involving the patient.
- Social determinants of health should be considered and inform the recommendations from treatment providers

Nutrition and Diet

Though the literature on nutrition and cardiovascular outcomes is limited by a relative paucity of prospective randomized controlled trials with long-term follow up and rigorously measured outcomes, clear themes emerge.

- Dietary elements that tend to increase risk include: sugar, low-calorie sweeteners, high-carbohydrate diets, trans fat, saturated fat, sodium, red meat, and processed red meat (e.g., bacon, salami, ham, hot dogs, sausage)
- The relationship between sodium consumption and cardiovascular disease risk in the general population is complicated; based on epidemiologic data, sodium restriction for addressing hypertension or when baseline sodium intake is high may be appropriate. Potassium consumption is inversely correlated with cardiovascular disease risk.
- Dietary fiber intake is inversely correlated with cardiovascular disease risk.

Recommended dietary changes:

- Diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish (IB)
- Diet low in cholesterol and sodium can be beneficial (IIB)
- Replacement of saturated fats with dietary monounsaturated and polyunsaturated fats can be beneficial (IIB)
- For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss.
- For adults with diabetes, a diet low in carbohydrates is recommended

Recommended to avoid:

- Minimize processed meats, refined carbohydrates, sweetened beverages in the diet
- Avoid intake of trans fats

Physical Activity and Exercise

Approximately half of all adults in America do not meet minimum physical activity recommendations. Aerobic physical activity is associated with reductions in ASCVD risk across many observational studies. Resistance exercise should also be encouraged for improving physical functioning, improving glycemic control in individuals with diabetes, and possibly lowering BP, but it is not known if resistance exercise lowers ASCVD risk.

- Adults should be routinely counseled to optimize a physically active lifestyle
- Adults should engage in at least 150 min/week of accumulated moderate-intensity or 75 min/week of vigorous-intensity aerobic physical activity to reduce ASCVD risk

- For adults unable to meet the minimum physical activity recommendations, engaging in some moderate- or vigorous-intensity physical exercise, even if less than the recommended amount, can be beneficial to reduce ASCVD risk
- Decreasing sedentary behavior in adults may be reasonable. On average U.S. adults spend >7 h/day in sedentary activities.

Tobacco Use

Tobacco use is the leading cause of disease, disability, and death in the United States.

- All adults should be assessed for tobacco use at every healthcare visit and their use-status recorded as a vital sign (IA)
- All adults who use tobacco should be firmly advised to quit (IA)
- A combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates (IA)
- It is reasonable to dedicate trained staff to tobacco treatment at every health center (IIB)
- All adults and adolescents should avoid secondhand smoke to reduce ASCVD risk (III)

Aspirin Use

Aspirin has long been the backbone medical therapy to reduce risk of ASCVD events, and its role in *secondary prevention* is clear. However, its role in primary prevention in the general population, particularly among non-diabetics, has been controversial. Furthermore, through its irreversible platelet inhibition, aspirin reduces risk of atherothrombosis, but increases risk of bleeding. The data supportive of aspirin in primary prevention is derived from studies in an era prior to aggressive risk factor reduction for hypertension, hyperlipidemia and tobacco cessation. However even in that era, multiple studies including the Physician's Health Study (1989) [3] and Women's Health Study (2005) failed to show mortality reduction with aspirin therapy for primary prevention, but there was suggestion of reduction in rates of MI [3, 4]. Furthermore, large meta-analyses demonstrated reduction in rates of ASCVD events, with increases in bleeding risk [5]. Based off of these and other conflicting data, various societies including the United States Preventive Services Task Force (USPSTF), the American Heart Association (AHA), American Diabetes Association (ADA), and the European Society of Cardiology (ESC) took different stances on the subject of aspirin, from recommending it in select populations at higher risk, to not recommending it at all for primary prevention [6].

In 2018, three pivotal trials on aspirin in primary prevention were published (See Table 5-2) [7]:

- **ASCEND** (A Study of Cardiovascular Events in Diabetes) [8]
  - Randomized 15,480 patients with DM without known CVD to either aspirin (100 mg/daily) or placebo, and assessed serious vascular events (MI, stroke/TIA or death from any vascular cause) with a mean follow up of 7.4 years
  - Serious vascular events occurred in significantly fewer individuals in the aspirin group (absolute risk reduction [ARR], 1.1%, rate ratio 0.88; $p = 0.01$)
  - This benefit was counterbalanced by an increased incidence of major bleeding events (absolute risk increase [ARI], 0.9%, rate ratio 1.29; $p = 0.003$).
- **ARRIVE** (Aspirin to Reduce Risk of Initial Vascular Events) [9]
  - Randomized 12,546 non-diabetic individuals with moderate CVD risk (defined as 10–20% 10-year risk) to either aspirin (100 mg/daily) or placebo and assessed for major adverse cardiovascular events (MACE) (reported as a composite endpoint of MI, unstable angina, stroke/TIA and time to cardiovascular death) with a mean follow up of 5 years.
  - No difference was demonstrated in risk of MACE.
  - An increase in gastrointestinal bleeding was observed with aspirin use (ARI 0.5%, HR 2.11).

TABLE 5-2

SUMMARY OF MAJOR TRIALS EVALUATING THE ROLE OF ASPIRIN IN CARDIOVASCULAR DISEASE AND MAJOR BLEEDING

STUDY	N	PRIMARY ENDPOINT	MI REDUCTION	STROKE REDUCTION	MORTALITY REDUCTION	INCREASE MAJOR BLEEDING RISK
Meta-analysis of RCT (Guirguis-Blake et al. 2016 Ann Intern Med)[a]	118,445	N/A	Yes	No	No	N/A
ASCEND (2018 NEJM)	15,480, DM	Positive	No	No	No	Yes
ARRIVE (2018 Lancet)	12,546, non-DM, moderate CVD risk	Negative	No	No	No	No
ASPREE (2018 NEJM)	19,114, ≥70 yo	Negative	No	No	No	Yes

[a]Trials conducted during a time when aggressive risk factor modification was not common

- **ASPREE** (Aspirin in Reducing Events in the Elderly) [10]
  - Randomized 19,114 elderly patients (>70 years-old) without known CVD to aspirin (100 mg/daily) or placebo and assessed for a composite of death, dementia, or persistent physical disability, with secondary endpoints that included major hemorrhage and cardiovascular disease (defined as fatal coronary heart disease, nonfatal MI, fatal or nonfatal stroke, or hospitalization for heart failure), with a median follow up of 4.7 years.
  - Aspirin did not achieve any difference in disability-free survival, nor did it result in a significantly lower rate of cardiovascular events.
  - Patients administered aspirin had higher rates of major hemorrhage (hazard ratio 1.38) primarily composed of upper gastrointestinal bleeding and intracranial bleeding. Aspirin administration was also associated with higher all-cause mortality primarily related to cancer-related deaths, which should be interpreted with caution.

Given the totality of these data the ACC/AHA advise **aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit**:

- Low-dose aspirin (75–100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40–70 years of age who are at higher ASCVD risk but not at increased bleeding risk
- Low-dose aspirin should NOT be administered routinely for primary prevention in adults >70 years of age
- Low-dose aspirin should NOT be administered for primary prevention of ASCVD among adults at increased risk of bleeding

HYPERTENSION

Hypertension is one of the most common pathologic entities in the world and is the leading cause of death and disability-adjusted-life-years globally. In this section, we review the pathophysiology, diagnosis, treatment, and outcomes related to hypertension.

In 2017, the AHA and ACC in conjunction with nine other major professional societies released their most updated clinical practice guidelines. The summary below generally follows the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA

Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017 ACC/AHA guideline) [11, 12].

Compared to the JNC8 guidelines from 2014, an important change in the current iteration is lowering the blood pressure threshold for the diagnosis of hypertension—now designated as a BP ≥130/80 mmHg, as opposed to ≥140/90 mmHg. As a result of this new definition, the estimated prevalence of U.S. adults with hypertension has risen substantially, from 72 million to 103 million, or 32–46% of the population, by one estimate. By changing the thresholds for hypertension, the 2017 ACC/AHA guidelines expanded the number of individuals now eligible for anti-hypertensive therapy, in addition to suggesting that more intensive BP lowering may be warranted for a subset of patients already on anti-hypertensive agents. In a further departure from previous guidelines, the decision to initiate anti-hypertensive therapy incorporates not only absolute BP values, but also a global assessment of cardiovascular risk.

Pathophysiology and Epidemiology of Hypertension

Essential Hypertension

- The great majority of hypertension (90–95%) of hypertension is essential hypertension (otherwise known as primary hypertension)
- The pathophysiology of essential hypertension is incompletely understood, but is thought to related to one or more of the following
  - Changes in the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS)
  - Renal dysfunction
  - Genetic and environmental factors

Hypertension and Aging

Epidemiology

- At age ≥70 years, ≈70% of men and women have hypertension, compared with <20% among those aged ≤44 years [13]
- The residual lifetime risk of hypertension among persons ≥60 years who do not yet have hypertension is ≈90% [14]
- Projections show that by 2030, ≈40% of US adults will have hypertension, an increase of 8.4% from 2012 estimates [13]

Differences in Systolic and Diastolic Blood Pressure

- With increasing age, systolic blood pressure (SBP) increases in all populations studied
- Diastolic blood pressure (DBP) increases until approximately the fifth or sixth decade and declines thereafter ([15], Fig. 5-1)
- The increase of blood pressure (BP) with age is more pronounced in women ([16], Fig. 5-2)

Isolated Systolic Hypertension (ISH)

- The great majority of older patients with hypertension have ISH, with diastolic hypertension occurring in a minority (10% among those aged 70)
  - ISH is primarily due to decreased compliance of the large arteries and increased pulse wave velocity
    - Corresponding age-related changes in the histology of the large vessels include a decrease in elastic fibers and replacement with collagen

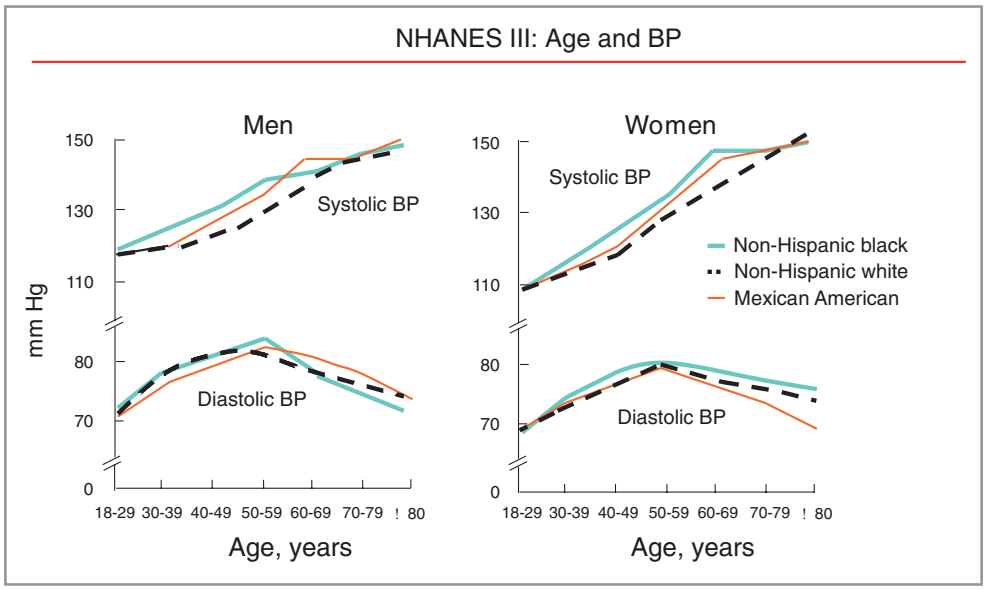


FIGURE 5-1

Changes in systolic and diastolic blood pressure with age (used with permission from [15])

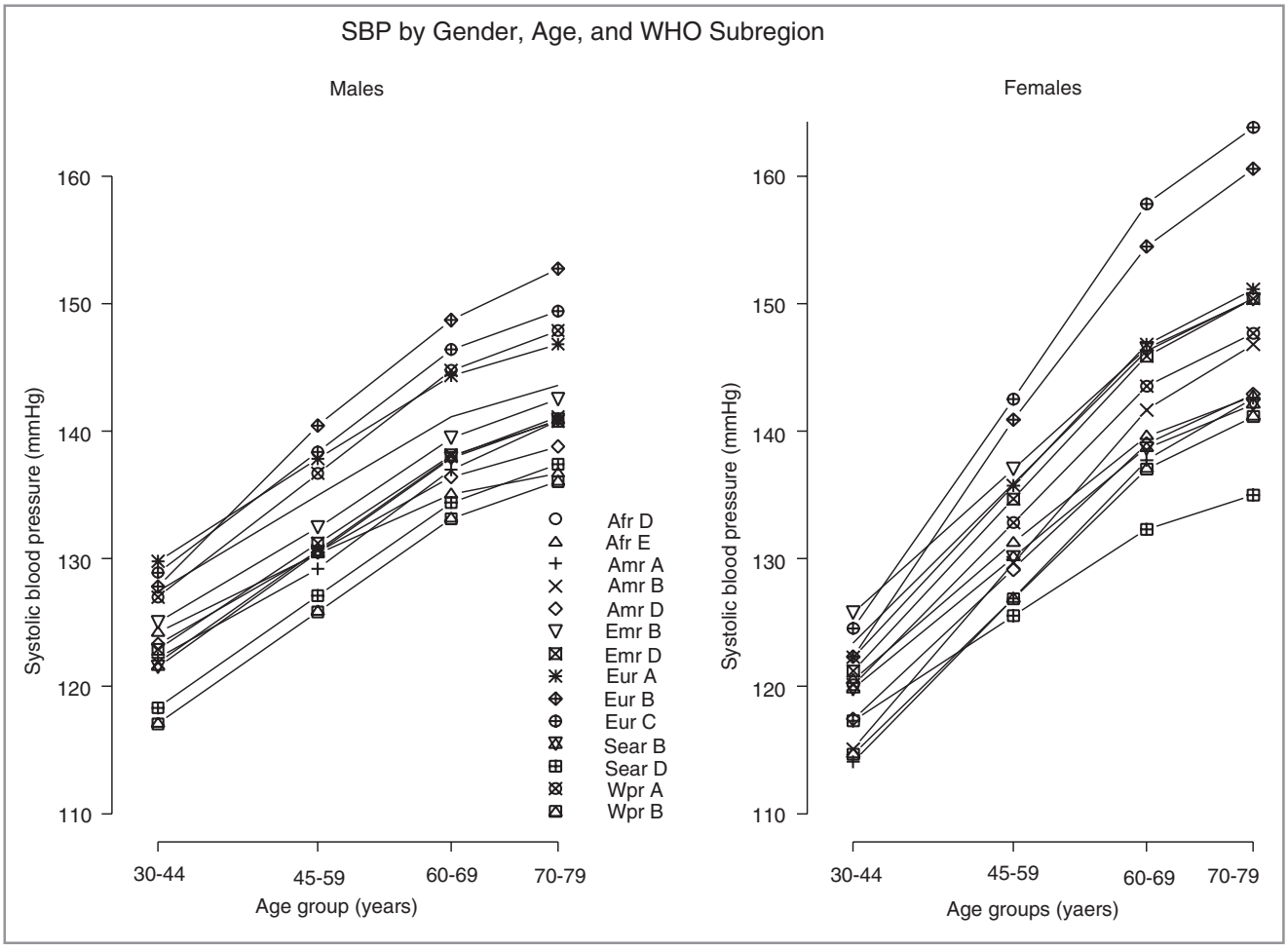


FIGURE 5-2

SBP by gender, age, and World Health Organization (WHO) subregion (used with permission from [16])

- ISH is a result of the following phenomena [17]:
  - Increased pulse pressure (due to central arterial stiffness) for a given stroke volume, with higher SBP and lower DBP
  - High pulse wave velocity, which results in the reflected pulse waves arriving at the central aorta during systole rather than after the dicrotic notch (as occurs in younger individuals)
  - Endothelial dysfunction, which results in impaired flow-mediated arterial dilation
- These physiologic and pathologic effects of aging are modulated to a significant extent by behavioral and environmental influences including physical activity, diet [18].

Additional Differences with Aging

- Aging is associated with downregulation and decreased responsiveness of beta-receptors, and increased ambient catecholamine concentrations
- Elderly hypertensives usually have low renin, low aldosterone, and salt-sensitive hypertension because of decreased natriuretic activity [19]
- Between the ages of 30 and 85, ~1/4 of the cortex is lost due to glomerulosclerosis and interstitial fibrosis [20]
- Polypharmacy
  - Polypharmacy and cost may result in decreased adherence to therapy
  - Polypharmacy in combination with decreased renal function increases the probability of drug interactions and adverse events
  - Increased use of *non-steroidal anti-inflammatory agents (NSAIDs)* among older patients (see Drug-Induced Hypertension)
- Orthostatic hypotension due to impaired baroreflex function

Secondary Hypertension (See Figs. 5-3 and 5-4)

Acute Kidney Disease

- Acute glomerular disease may result in volume retention and hypertension due to increased sodium reabsorption
- Acute vascular injury due to vasculitis or connective tissue disease (e.g. SLE, scleroderma) may induce hypertension by increased activation of the RAAS triggered by ischemia

Chronic Kidney Disease (CKD)

- Many causes of CKD may lead to hypertension through sodium retention and volume expansion, increased activity of the RAAS due to ischemia, and enhanced sympathetic tone

Renovascular Hypertension

- Usually related to renal artery stenosis due to atherosclerosis of the large renal arteries or their ostia
  - When stenosis exceeds 70% of the diameter (about 90% reduction in cross-sectional area), a potentially hemodynamically significant decrease in blood flow results in decrease of intraglomerular pressure with subsequent activation of the RAAS and increased sodium reabsorption
- Renal artery stenosis is a manifestation of widespread atherosclerosis that may involve other arterial beds (cerebrovascular, coronary, peripheral) [21, 22]
- In clinical trials of patients with renal artery stenosis, there has not been a marked clinical benefit from revascularization procedures

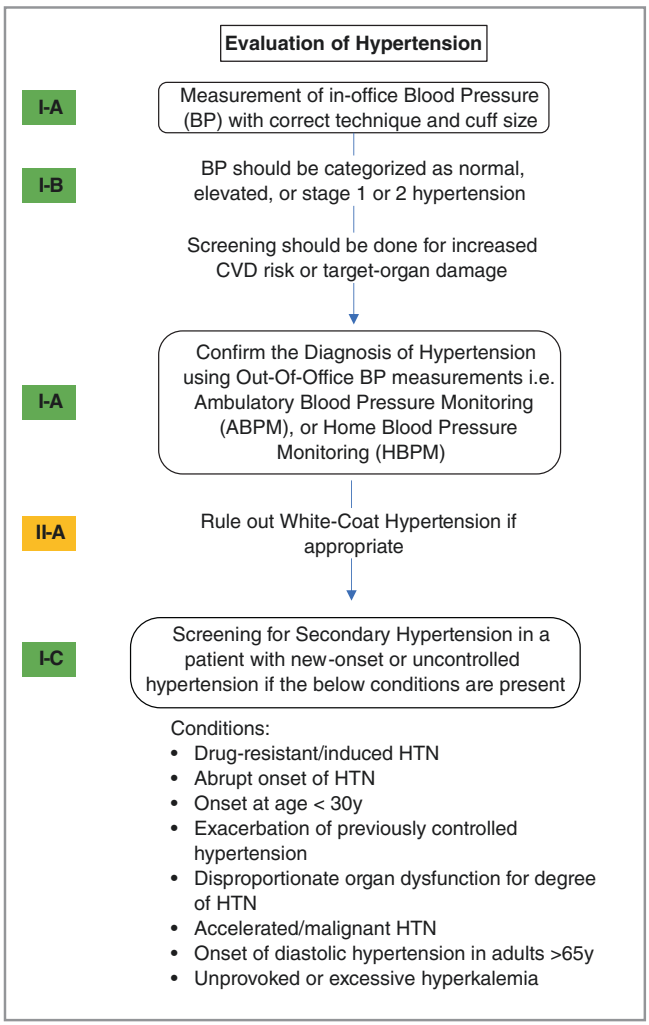


FIGURE 5-3

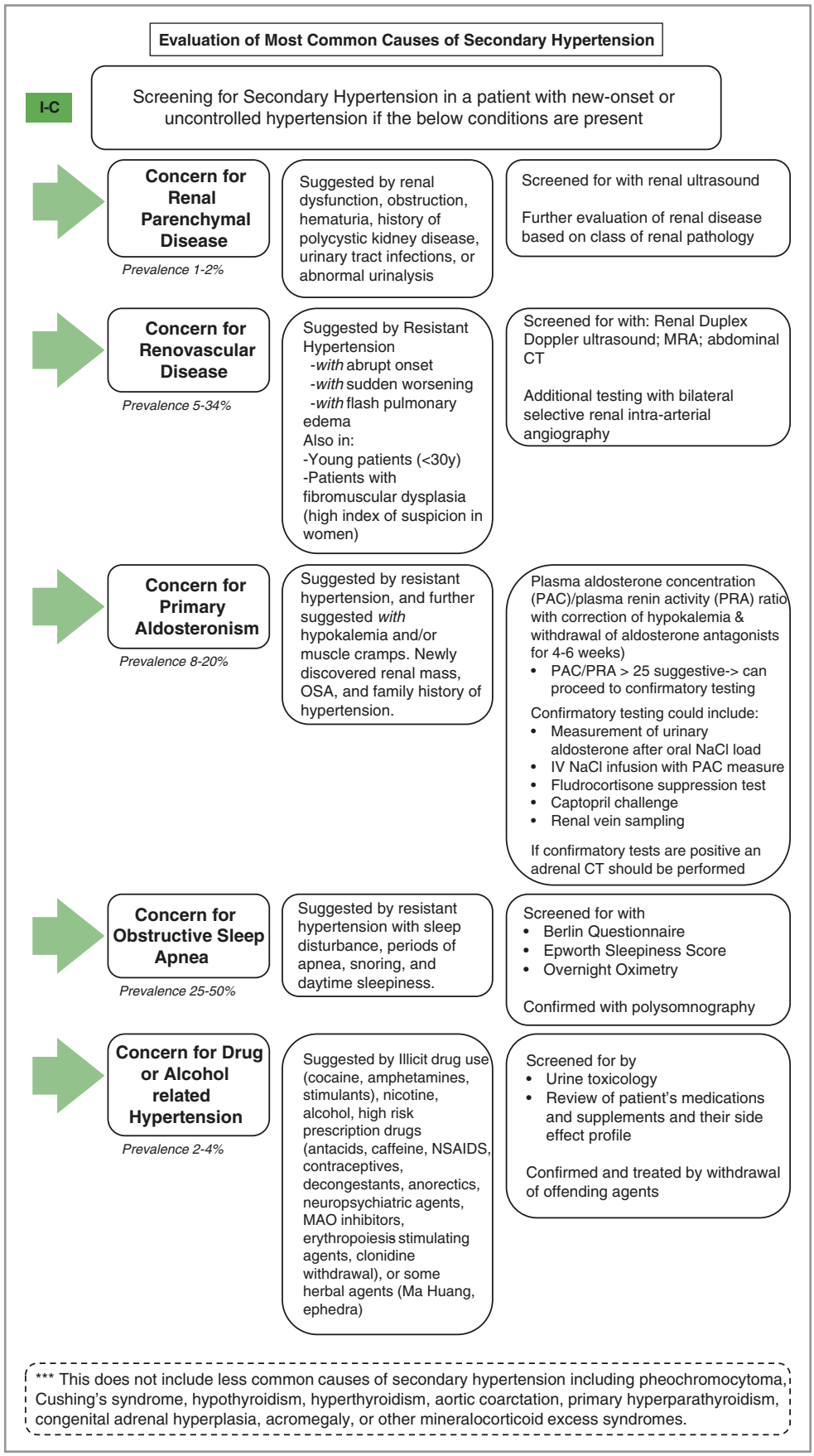
Evaluation of hypertension as per recommendations set forth in the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Primary Aldosteronism (PA)

- Relatively common cause of **resistant hypertension** (hypertension despite the use of at least three antihypertensives)
- Usually associated with *adrenal hyperplasia (usually bilateral) or an adrenal adenoma*
- May also be caused by familial hyperaldosteronism, adrenal carcinoma, or ectopic aldosterone-producing tumors
- Diagnostic clues include **suppressed plasma renin activity, high aldosterone**, and **hypokalemia (may not be present)** in a hypertensive patient [22]
- Diagnostic approach includes measurement of
  - Plasma renin activity (PRA), plasma renin concentration (PRC), and plasma aldosterone concentration (PAC)
  - **PAC/PRA ratio >25 suggests PA, while normal and hypertensives without PA have ratios <10** (should be assessed with correction of hypokalemia and withdrawal of aldosterone antagonists for 4–6 weeks)
- If PAC/PRA ratio suggests PA, one or more confirmatory tests should be performed: [23]
  - Urinary aldosterone excretion after oral sodium chloride loading (>12 μg/24 h after 200 mmol/day (~6 g/day) sodium intake)

FIGURE 5-4

Evaluation of the most common causes of secondary hypertension



- PAC after IV sodium chloride loading (PAC > 10 ng/dL after infusion of 2 L normal saline over 4 h)
- Fludrocortisone suppression test (upright PAC > 6 ng/dL after 4 days)
- Captopril challenge (PAC, normally suppressed by 25–50 mg of captopril, remains elevated, while PRA remains low)
- Note: Certain medications (e.g. *aldosterone receptor antagonists or mineralocorticoid receptor antagonists (MRA)) must be held during testing*

- If confirmatory tests are positive, patients should undergo **adrenal CT**
- Selective adrenal vein sampling may be used to distinguish unilateral from bilateral adrenal involvement in cases where surgery (unilateral adrenalectomy) is an option
- For unilateral adrenal involvement or for extra-adrenal lesions, surgical resection is often primary therapy
- Medical treatment (e.g. for bilateral adrenal hyperplasia) is based on the use of **MRA**s

Thyroid Disease

- Both hyperthyroidism and hypothyroidism may be associated with hypertension.

Cushing's Syndrome

- **Increased ACTH levels**, whether iatrogenic, from adrenal tumors, or from other paraneoplastic activity, can lead to hypertension, which may be severe

Pheochromocytomas

- Rare catecholamine-producing tumors that can cause paroxysmal hypertension

Aortic Coarctation

- Congenital abnormality that leads to predominately *upper-extremity hypertension* secondary to mechanical obstruction (typically distal to the brachiocephalic circulation)

Obstructive Sleep Apnea (OSA)

- Obstructive sleep apnea is a common chronic condition characterized by recurrent collapse of upper airways during sleep, inducing intermittent episodes of apnea/hypopnea, hypoxemia, and sleep disruption [24]
- OSA should be treated due to a variety of sequelae, including fatigue, systemic and pulmonary hypertension, and all-cause and CAD-related mortality
- Multiple causative mechanisms for hypertension have been proposed including (1) repetitive hypoxemia and hypercapnia cycles causing autonomic changes and increased catecholamine levels, (2) systemic inflammation induced by OSA, (3) effects on both the micro and macro vasculature.
- Though use of **continuous positive airway pressure (CPAP)** has been well-established to treat OSA, in adults with concomitant hypertension and OSA, the effectiveness of CPAP to reduce BP is less well-established but data generally suggests benefit [12, 25, 26]

Drug-Induced Hypertension

- Medication use is an important cause of secondary hypertension
  - Causes include **NSAIDs, stimulants, and sympathomimetic decongestant agents and oral contraceptive pills**.
    - Inhibition of prostaglandins may result in decreased renal function, sodium and water retention, BP elevation, and HF
    - *NSAIDs may impair the BP-lowering effect of ACE inhibitors, ARBs, and diuretics*

Diagnosis of Hypertension

Definitions of Hypertension (Table 5-3) [17]

Per the 2017 ACC/AHA guideline:

- **Normal BP:** Systolic <120 mmHg and diastolic <80 mmHg
- **Elevated BP:** Systolic 120–129 mmHg and diastolic <80 mmHg
- **Stage 1 hypertension:** Systolic 130–139 mmHg or diastolic 80–89 mmHg
- **Stage 2 hypertension:** Systolic ≥140 mmHg or diastolic ≥90 mmHg
- BP Target
  - **For patients with 10-year ASCVD risk >10%, ASCVD, DM, or CKD, a goal of <130/80 mmHg is recommended**
- Therapy
  - For patients with Stage 1 Hypertension
    - If 10-year ASCVD risk <10%, then non-pharmacological therapy is recommended
    - If 10-year ASCVD risk >10%, then medication plus lifestyle changes are recommended for a goal of <130/80 mmHg
  - For patients with Stage 2 Hypertension
    - Medication plus lifestyle changes are recommended
    - In patients with Stage 2 Hypertension, >20/10 mmHg above target BP of 130/80, it is recommended to start two antihypertensive medications of different classes.
- To-date, the most significant contemporary trial to impact these guidelines was the Systolic blood PRessure Intervention Trial (**SPRINT**) which enrolled nearly 10,000 patients at increased risk of CV events, but **without diabetes** and randomized them to a systolic blood pressure target of <120 mmHg (intensive control) versus <140 mmHg (standard treatment) [27].
  - The trial was stopped early at a median follow up of 3.26 years due to a significantly lower rate of the primary composite outcome (MI, other ACS, stroke, HF or death from other CV causes) in the intensive-treatment arm (hazard ratio 0.75).
    - Primary outcome primarily driven by a reduction in CHF risk, and no significant reduction in MI or stroke was observed
  - All-cause mortality was also lower in the intensive treatment arm (hazard ratio 0.73).
  - Rates of serious adverse events (including hypotension, syncope, electrolyte abnormalities, and AKI) were also were higher in the intensive treatment group, though interestingly rates of injurious falls were not higher in the intensive treatment group compared to standard treatment
  - Notably 28% of patients in each group were older than age 75

TABLE 5-3

CATEGORIES OF BLOOD PRESSURE IN ADULTS

BP CATEGORY	SBP	DBP
Normal	<120 mmHg	<80 mmHg
Elevated	120–129 mmHg	<80 mmHg
Hypertension		
Stage 1	130–139 mmHg	80–89 mmHg
Stage 2	≥140 mmHg	≥90 mmHg

[a]Individuals with SBP and DBP in two categories should be designated to the higher BP category
[b]BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions)

Techniques

- It is important to measure the blood pressure in a comfortable position after sitting with feet supported for *at least 5 min*. Hypertension should be confirmed with out-of-office assessments of blood pressure.
- Home BP monitoring
  - Although Ambulatory BP monitoring (ABPM) is generally considered the best out-of-office method, home BP monitoring can be a more practical approach.
- Ambulatory BP monitoring
  - Ambulatory BP is a **predictor of target organ damage as well as outcomes that surpasses office BP** [28]
  - Ambulatory BP measurement is now **recommended in the National Institute for Health and Clinical Excellence (UK) as well as in the 2017 ACC/AHA guidelines to confirm the diagnosis following an initial elevated BP measurement in the clinic** [29].

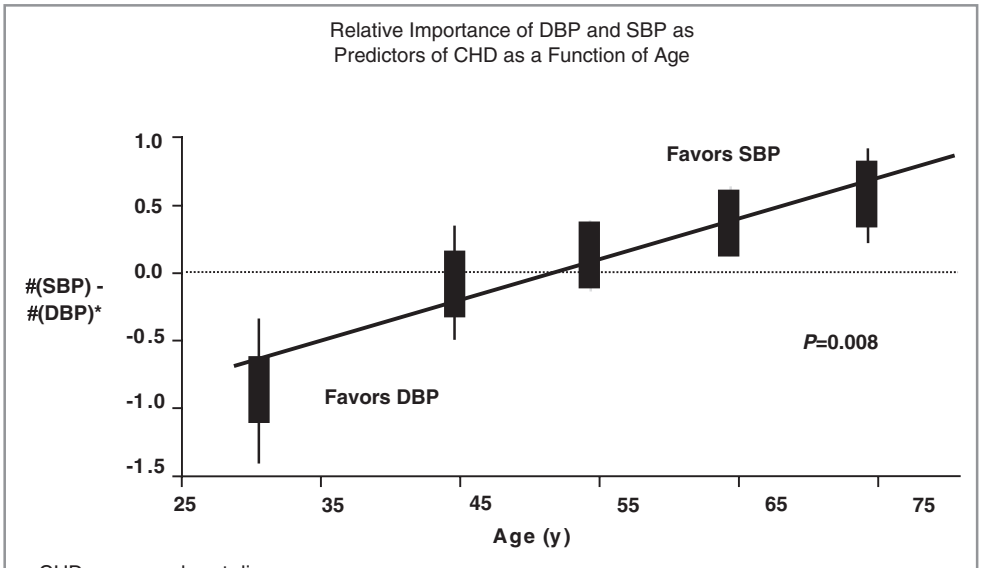
Association with Risk

- Data from the Framingham Heart Study showed that in younger ages, DBP is more important in determining risk of CHD while in older individuals, the risk primarily is determined by SBP ([30], Fig. 5-5)
- Overall, both SBP and DBP are independently associated with CVD risk [31].
- Pulse pressure is separately associated with CVD risk in older individuals [32]

Sequelae of Hypertension

Target Organ Damage

- End-organ damage can occur with long-standing poorly controlled hypertension
- Hypertension is an important *risk factor for the development of abdominal and thoracic aortic aneurysm and aortic dissection*



CHD, coronary heart disease.
*The difference between SBP and DBP proportional hazard regression coefficients, ie, #(SBP) - #(DBP), was estimated for each age group.
Franklin SS et al. *Circulation*. 2001;103:1245-1249.

FIGURE 5-5

Relative importance of DBP and SBP as predictors of CHD as a function of age (used with permission from [31])

- *Hypertensive retinopathy* with arteriovenous nicking, arteriolar narrowing, and in some cases hemorrhages, exudates, and papilledema increases in frequency with age and SBP.
- *Hypertensive Nephropathy* leads to renal tubular dysfunction and reductions in renal function

Morbid and Mortal Events

- Hypertension accounts for more attributable deaths worldwide than any other risk factor, whereas smoking and high cholesterol are second and third, respectively [1]
- The causes of death related to hypertension are **CHD, stroke, HF, and CKD**, especially when hypertension coexists with *diabetes mellitus* [33]
  - Age is a major determinant of risk for cardiometabolic diseases
  - BP tends to increase with age and the corresponding relative risk imposed by a given BP level decreases with age—this may be related to changes in the vasculature or confounding from survival bias in the literature
    - For patients aged 50–59 years, the relative risk for fatal stroke is approximately 16 for patients with SBP of 180 mmHg compared to those with SBP of 110 mmHg, while for patients aged 80–89 years, the relative risk is approximately 2.
    - On the other hand, the increase in absolute risk for mortality from stroke is greater in older individuals ([34], Fig. 5-6, left panel).

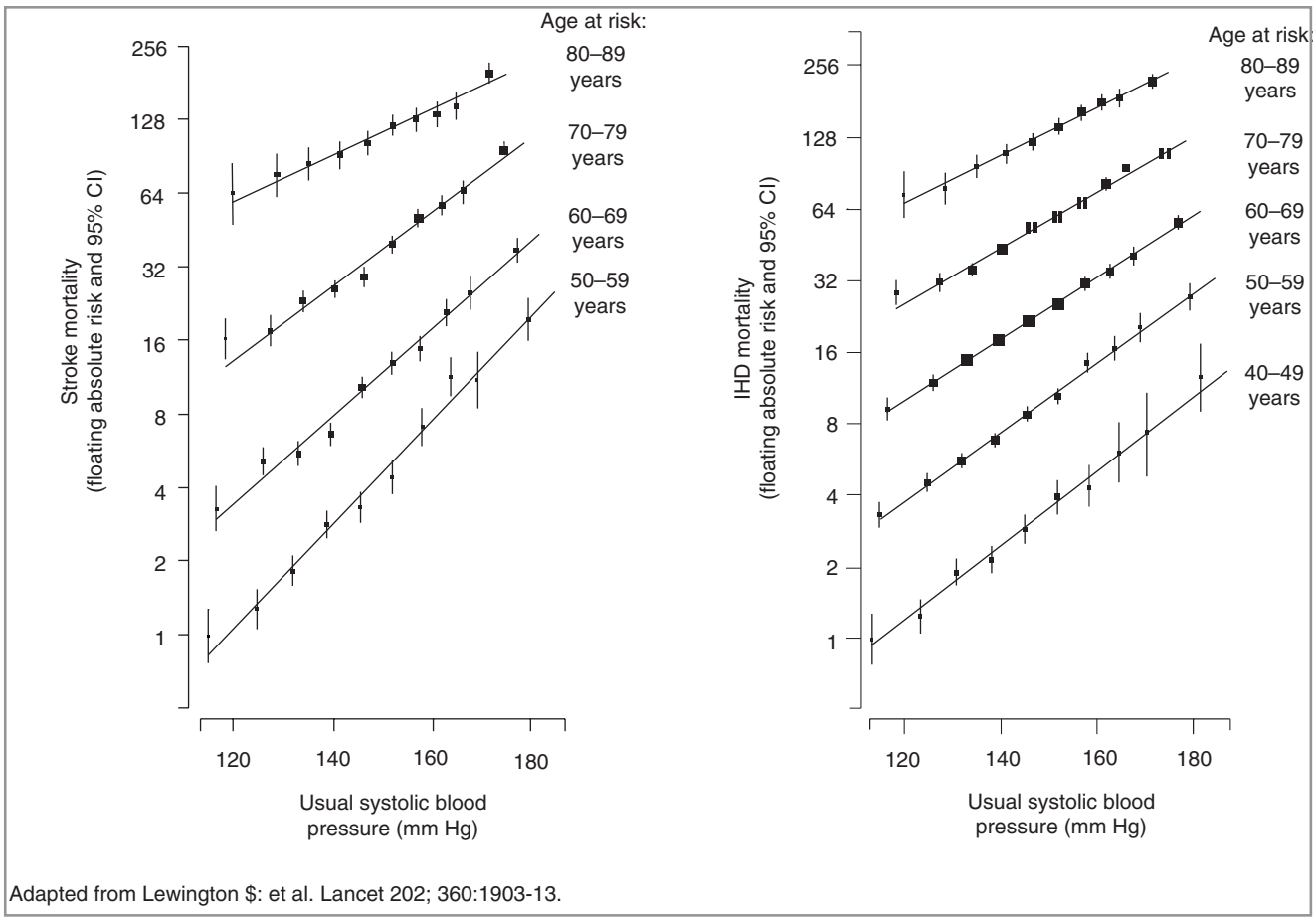


FIGURE 5-6

Cardiovascular disease mortality with increasing SBP by age (used with permission from [33])

Hypertension and Heart Failure

- Left ventricular systolic dysfunction (LVSD), LV diastolic dysfunction and HF are common complications of aging and hypertension
- Treatment of ISH with **chlorthalidone-based diuretic therapy resulted in marked decrease in HF risk** in the Systolic Hypertension in the Elderly Program (SHEP) [35]
  - The occurrence of HF was related to SBP, as well as to pulse pressure independently of SBP.
- Uncontrolled hypertension and aging interact to exacerbate the development of HF, especially in the presence of obesity or diabetes, which further contribute to increased LV mass, LV wall thickness, and abnormal diastolic LV filling patterns
- Adaptive and maladaptive responses to myocardial infarction may also be altered by uncontrolled hypertension leading to increased risk for HF

Treatment of Hypertension

Non-pharmacologic Strategies

- Lifestyle changes alone are recommended for most adults newly classified as having stage 1 hypertension (130–139/80–89 mmHg), and lifestyle changes plus drug therapy are recommended for those with existing CVD or increased CVD risk (>10% 10-year ASCVD risk).
- Among those with stage 2 hypertension (>140/90 mmHg), both lifestyle changes and drug therapy are recommended
- Nonpharmacologic therapy may delay the need for pharmacologic therapy in some and may facilitate control of BP with lower doses of or fewer medications
  - **Weight loss, sodium reduction,** and their combination were found useful in controlling hypertension without pharmacotherapy in older hypertensive patients who needed one or two medications for control [36]
  - In Western countries, *enhanced dietary potassium consumption* may yield more clinical efficacy than sodium restriction [37]
  - **Excessive alcohol consumption** is associated with increased BP, potentially due to sympathetic activation and cortisol increase
- The effect of antihypertensive therapy in decreasing cardiovascular events is more pronounced when BP reduction is greater [38]

Differing Patient Subsets

- Among the medications approved for control of hypertension, thiazide diuretics, ACE inhibitors (ACEi), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) may be used as a first line drug in patients with hypertension (Table 5-4)
- A number of coexisting conditions as well as demographic differences may alter the preferred agents used to treat hypertension and the BP targets to be achieved
- Adverse effects of medications become important in different patient subsets (e.g. bronchospastic disease for beta-blockers)
  - In older patients, treatment with diuretics is associated with **hyperglycemia** whereas treatment with CCBs is neutral, and treatment with ACEi/ARB is associated with lower blood glucose levels [39]
  - Thiazide-type diuretics produce hyperglycemia in part by impaired insulin release related to hypokalemia rather than through insulin resistance, the common mechanism of diabetes in older adults
  - Both hypertension and diuretic use increase the chance of developing **gout** (Fig. 5-7)

TABLE 5-4

FIRST AND SECOND LINE ORAL ANTIHYPERTENSIVE DRUGS AS LISTED IN THE 2017 ACC/AHA GUIDELINES

CLASS OF AGENT	EXAMPLE DRUG	CONSIDERATIONS FOR USE
Primary agents		
Thiazide diuretics	Chlorthalidone Hydrochlorothiazide Metolazone Indapamide	– Chlorthalidone preferred due to prolonged half-life and trial-proven reductions in CVD – Monitor for hyponatriemia, hypokalemia, and acute gout (consider uric acid lowering therapies)
ACEi/ARB	Enalapril Lisinopril Captopril Losartan Irbesartan Valsartan Irbesartan	– May offer renal protection in patients with CKD and diabetes – Do not use ACEi/ARB in combination or with a direct renin inhibitor. – Avoid if history of angioedema – Risk of ARF in patients with bilateral severe RAS – Increased risk of hyperkalemia in CKD – Do not use in pregnancy
Dihydropyridine CCBs	Amlodipine Nifedipine	– Avoid use in HFrEF – Dose related pedal edema
Nondihydropyridine CCBs	Diltiazem Verapamil	– Avoid routine use with beta blockers due to increased incidence of bradycardia and heart block – Do not use in patients with HFrEF – Diltiazem and Verapamil have drug interactions through the CYP3A4 mechanism
Secondary agents		
Loop diuretics	Furosemide Bumetanide Torsemide	– Preferred diuretics in symptomatic HF – Preferred over thiazide diuretics in moderate-to-severe CKD (GFR < 45 mL/min)
Aldosterone Antagonists	Eplerenone Spironolactone	– Preferred agents in primary aldosteronism and resistant hypertension – Spironolactone is associated with a greater risk of gynecomastia and impotence – To be avoided in conjunction with potassium supplements or K-sparing diuretics, or significant CKD
Beta blockers	*Cardioselective* Atenolol Bisoprolol Metoprolol *Vasodilatory* Nebivolol *Nonselective* Nadolol Propranolol *Alpha/Beta Blocker* Carvedilol Labetalol	– No longer first line agents – Only first-line in patients with ischemic heart disease or heart failure – Cardioselective BB are preferred with bronchospastic airway disease – Bisoprolol, Metoprolol and Carvedilol are preferred in patients with HFrEF – Nebivolol induces Nitric Oxide induced vasodilation – Avoid abrupt cessation of all beta blockers
Potassium-sparing diuretics	Amiloride Triamterene	– Monotherapy agents and minimally effective anti-hypertensive agents – Combination therapy with a thiazide diuretic can be considered in patients with hypokalemia on a thiazide – Avoid in patients with significant CKD
Direct renin inhibitors	Aliskerin	– Very long acting – Increased risk of hyperkalemia. Do not use in CKD – Do not use in combination with ACEi/ARB
Alpha-1 blockers	Doxazosin	– Associated with orthostatic hypotension – Second line in patients with concomitant BPH

TABLE 5-4

(CONTINUED)

CLASS OF AGENT	EXAMPLE DRUG	CONSIDERATIONS FOR USE
Direct vasodilators	Hydralazine Minoxidil	– Associated with sodium and water retention and reflex tachycardia; *best used with diuretic and beta blocker* – Hydralazine is associated with a drug-induced lupus syndrome at higher doses – **Minoxidil is associated with hirsutism, requires a loop diuretic, and can induce pericardial effusion**
Central alpha-2 agonist	Clonidine	– Generally reserved as last-line because of significant CNS adverse effects, especially in older adults – Abrupt discontinuation can induce hypertensive crisis, and thus clonidine must be tapered off

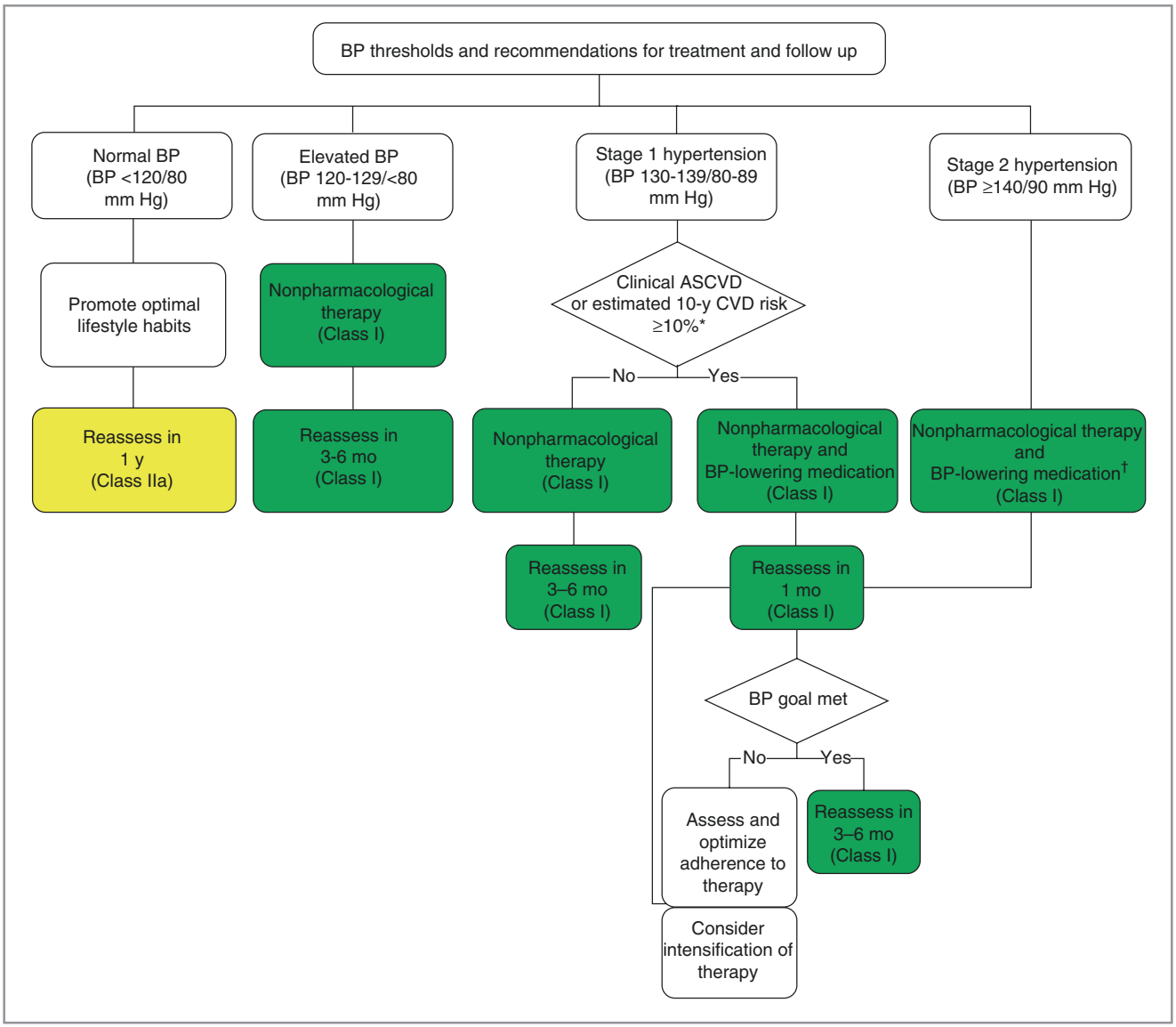


FIGURE 5-7

Blood pressure (BP) thresholds and recommendations for treatment and follow up (used with permission from [12])

Special considerations

- **Older adults** (>65 years of age) have a recommended treatment goal of <130/80 mmHg when their 10-year CVD risk is >10%
  - Multiple RCTs have also shown that hypertension treatment can be safely escalated among older adults living in the community with a reduction in cardiovascular disease risk.
- In the U.S., **older Black Americans** have more severe hypertension and have high rates of stroke, LVH and CKD
  - Blacks in NHANES III were less likely to have their BP controlled. They are also more likely to have diabetes and increased BMI.
  - Blacks are more likely high-volume/low-renin hypertensives, and hence **diuretics as well as CCB** are reasonable agents to use
- **Women who are pregnant or planning to become pregnant** and require treatment should be transitioned to **methyldopa, nifedipine, and/or labetalol** during pregnancy.

Resistant Hypertension

- Definition: BP above goal despite the concurrent use of three antihypertensive medications of different classes (a diuretic should be one class)
- Occurs in about 13% of patients based off the previous definition of >140/90 mmHg
  - Causes include secondary hypertension, such as renal artery stenosis, as well as medication induced hypertension
- Risk factors include age, obesity, CKD, black race, and DM.
- Carries high CV risk as it is associated with severe hypertension, DM, CKD.
- **Pseudoresistance refers to lack of control due to poor adherence, white coat hypertension, lack of appropriate medication dose titration, etc.**
- Clinical evidence suggests that addition of a thiazide diuretic and/or MRA such as spironolactone in those with resistant hypertension is an effective intervention
- Additional antihypertensive classes that may be helpful as third-fifth line agents include
  - **MRA** (e.g. spironolactone, eplerenone), with particular benefit in HF
  - **Beta blockers**, particularly in those with ischemic heart disease or heart failure as guideline-directed management and therapy (GDMT), and in those with thoracic aortic disease.
  - **Hydralazine**, a peripheral vasodilator, which can be especially effective in combination with a beta blocker and diuretic such as spironolactone given **reflex tachycardia** and risk of fluid retention
  - **Minoxidil** (another peripheral vasodilator) is also used to **prevent hair loss**
  - **Centrally-acting alpha-2 agonists** (e.g. clonidine, alpha-methyldopa (also useful during **pregnancy** or for pregnancy-induced hypertension due to lack of teratogenicity))
  - **Alpha-blocking agents** (e.g. doxazosin (had higher incidence of HF in ALLHAT), phentolamine (for hypertensive emergency))
  - **Renal Denervation**—the data are largely neutral and it is not currently a recommended strategy. However, recent data indicates there may be a role for selected patients in the future.

Severe/Malignant Hypertension and Hypertensive Crises

- Hypertensive crisis refers the sudden or rapid development of severe hypertension (SBP $\geq$ 180 mmHg and/or DBP $\geq$ 120 mmHg)
- A hypertensive crisis constitutes a hypertensive emergency when the patient develops end-organ complications

- Management of hypertensive emergency involves immediate control of BP using intravenous antihypertensives
  - *(1) Lower BP by max 25% over the first hour*
  - *(2) Then aim for 160/100–110 over the next 2–6 h*
  - *(3) Lower to normal over the next 24–48 h*
  - Exceptions:
    - **Aortic dissection**: reduce SBP to <120 mmHg in the first hour
  - **Severe preeclampsia, eclampsia, or pheochromocytoma crisis**: reduce SBP to <140 mmHg in the first hour
- Hypertensive urgency refers to a hypertensive crisis *without symptoms* or the above acute target organ damage
  - Reduce blood pressure more gradually with oral agents

Questions and Answers

Question 1
A 45-year-old woman with type 2 diabetes mellitus, hypertension, and diverticulosis presents to the clinic for routine follow up care. Her physical exam reveals a heart rate of 72 bpm, blood pressure of 126/65 mmHg, and normal cardiovascular exam. Her labs demonstrate a hemoglobin A1c of 7.2%, and a serum creatinine level of 1.23 mg/dL. Urinalysis demonstrates 1+ proteinuria.

The preferred first-line antihypertensive treatment strategies for this patient includes:

A. ACE inhibition
B. Angiotensin receptor blockade
C. Direct renin inhibition
D. Aldosterone antagonist
E. All of the above
F. A and B only

Answer 1
Correct answer: F

In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mmHg or higher with a treatment goal of less than 130/80 mmHg. Per the 2017 ACC/AHA Guidelines, in diabetic patients with hypertension all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. Additionally, ACEI have been shown to confer nephroprotection in patients with both type 1 and type 2 DM, where they slow progression of microalbuminuria and may decrease blood glucose and the progression of retinopathy. There is a wealth of evidence supporting the use of ARBs in DM. Clinical trials such as RENAAL (losartan) and IDNT (irbesartan) showed evidence of nephroprotection in patients with DM type 2 and nephropathy. The ALTITUDE clinical trial of aliskiren vs. placebo on background therapy of ACEI or ARB in patients with type 2 DM and renal impairment was stopped by the DSMB because of **higher rate of adverse events without benefit with the direct renin inhibitor aliskiren**. Although spironolactone and eplerenone have shown mortality benefits in patients with HF and CHD and these agents may be included in combination therapy of hypertensive patients with DM, there are no large clinical trials demonstrating nephroprotection. A presumed superiority of ACEI and ARB on cardiovascular and all-cause mortality in patients with DM has not been proven in large clinical trials such as ALLHAT or meta-analyses.

Question 2

A 28 year-old man with a past medical history of depression and appendicitis presents as a referral from his primary care doctor for hypertension. His physical exam reveals a heart rate of 58 bpm, blood pressure of 172/78 mmHg, and normal cardiovascular exam. His labs demonstrate a hemoglobin A1c of 5.1%, and a serum creatinine level of 1.10 mg/dL, and a plasma aldosterone concentration to plasma renin activity ratio of 28. Which of the following may help to confirm the diagnosis?

A. Aldosterone levels after IV sodium chloride loading
B. Aldosterone levels after high dose oral salt intake
C. Selective adrenal vein sampling
D. Supine and upright posture renin-aldosterone profiling
E. All of the above

Answer 2

Correct answer: E

Common diagnoses to consider are bilateral adrenal hyperplasia and aldosterone-producing adenomas, but ectopic aldosterone-producing tumors, familial hyperaldosteronism types 1 and 2, and aldosterone-producing adrenocortical carcinomas should also be considered. Aldosterone levels after IV sodium chloride loading (2 L of isotonic saline over 4 h) in a patient who is resting lying down) as well as aldosterone levels after high dose oral salt intake (200 mmol (~6 g) sodium diet for 3 days) may be used to confirm primary hyperaldosteronism. Lack of suppression of the plasma aldosterone concentration to below 10 ng/dL (277 pmol/L) or urine aldosterone excretion >12 mcg/24 h (33 nmol/day) are consistent with primary aldosteronism (see Fig. 5-4). Selective adrenal vein sampling is the most definitive way to differentiate between bilateral adrenal hyperplasia and unilateral aldosterone producing adenomas. In the latter, there is more than fourfold difference in venous plasma aldosterone concentration between the two sides, while there is no significant difference in the former. This test is ordinarily performed before surgery, especially when a diagnosis cannot be made by CT or other means. *Each of the tests listed would likely follow initial screening with PAC/PRA testing.*

Question 3

A 62 year-old woman with a past medical history of rheumatoid arthritis and recurrent small bowel obstructions presents to clinic for follow up on a previously elevated blood pressure value. Her physical exam today is notable for a heart rate of 75 beats per minute, a blood pressure of 144/92 mmHg, a BMI of 29, and a normal cardiac exam. Her laboratory investigation is notable for a serum creatinine of 1.23, sodium of 136, and serum potassium of 4.4. Which of the following classes of medications could be recommended as suitable first-line therapies?

A. Thiazide diuretics
B. Beta blockers
C. ACE inhibitors
D. Angiotensin receptor blockers
E. Calcium channel blockers
F. All of the above
G. All of the above except B

Answer 3

Correct Answer: G

First-line agents for the treatment of hypertension are preferentially those agents that have been shown to reduce clinical events. In the 2017 guideline the following classes are considered first-line: **thiazide diuretics, ACE inhibitors, ARBs, and CCBs**. Other drug classes lack the same degree of evidence of reduction in clinical outcomes, or safety and tolerability relegating their role to use as secondary agents. In particular, there is inadequate

evidence to support the initial use of beta blockers for hypertension in the absence of specific cardiovascular comorbidities.

Furthermore, when therapy is being initiated, consideration should be given to starting with two drugs of different classes for those with stage 2 hypertension.

Question 4

A 72 year-old woman with a past medical history of hyperlipidemia, osteoarthritis and fibromuscular dysplasia presents is admitted to the hospital from clinic for hypertensive urgency. Her primary care doctor notes that she has never previously had a history of hypertension, but in the last several months has required sequential addition of multiple antihypertensive drugs. On physical exam she has a heart rate of 82 beats per minute, a blood pressure of 188/104 mmHg, and crackles on pulmonary auscultation. You note that a renal vascular ultrasound was performed which identified increased velocities in the right renal artery suggestive of severe unilateral renal artery stenosis. Which of the following drug classes are contraindicated?

A. ACE inhibitors
B. Angiotensin receptor blockers
C. Direct renin inhibitors
D. All of the above
E. None of the above

Answer 4

Correct answer: E

ACEI and ARB are effective in controlling BP alone or in combination with diuretics or CCBs. A major problem is a decrease in intraglomerular pressure due to ACEI/ARB-induced dilatation of the efferent arterioles with decrease in GFR and increase in serum creatinine (which should be monitored). Progression of the stenosis(es) and loss of renal parenchyma with worsening of renal function are additional concerns.

DIABETES MELLITUS AND THE METABOLIC SYNDROME

Diabetes mellitus (DM) significantly increases risk for atherosclerotic cardiovascular disease, and cardiovascular disease (CVD) is the most frequent cause of death among patients with DM. Coronary artery disease in diabetic patients is often more complex and widespread, thereby complicating management considerations. Patients with DM also suffer from an array of both microvascular and macrovascular complications. However, the increased cardiovascular risk seen in these patients can be modified by lifestyle interventions and pharmacologic measures, as evidenced by several large clinical trials. Furthermore, newer classes of antidiabetic medicines recently were shown to reduce cardiovascular death in the setting of DM and CVD.

Definitions and Classifications

Classification of DM

- **Type 1 diabetes (T1D)** results from destruction of pancreatic beta cells, which make insulin. Because the cause of diabetes is absolute lack of insulin, type 1 diabetics generally require insulin. *The absence of pancreatic autoantibodies does not rule out T1D.*
  - An uncommon subset includes **latent autoimmune diabetes in adults (LADA)** where circulating autoantibodies lead to beta cell destruction later in life, resulting in a delayed presentation of a type 1 phenotype
- **Type 2 diabetes (T2D**) results from a combination of insulin resistance and impaired beta cell function. Historically, insulin resistance had been considered the primary defect

in T2D. However, recent work highlights diverse mechanisms, including insulin secretory response.

- **Gestational diabetes** is diagnosed during pregnancy. Gestational diabetes generally resolves following pregnancy, but affected women are *at increased risk for developing T2D later* in life compared to unaffected women.
- **Other medical causes** include pancreatic tissue destruction (for example, from *cystic fibrosis, chronic pancreatitis, pancreatic tumors, or surgery), medications, and HIV-1 infection.*

Diagnosis of T2D

- According to the American Diabetes Association (ADA), a person can be diagnosed with T2D in any one of four ways [40]:

1. Fasting glucose ≥ 126 mg/dL
2. Hemoglobin A1c ≥ 6.5%
3. Glucose 2 h after oral glucose (75 g) tolerance test ≥200 mg/dL
4. Random glucose ≥200 mg/dL with classic symptoms (e.g., polyuria, polydipsia, and unexplained weight loss)

Prediabetes

- Prediabetes reflects increased risk for diabetes [41], and is defined as the presence of at least one of these three criteria:

1. Fasting glucose 100–125 mg/dL
2. Hemoglobin A1c 5.7–6.5%
3. Glucose 2 h after oral glucose (75 g) tolerance test 140–200 mg/dL

Metabolic Syndrome

- The metabolic syndrome refers to the co-occurrence of several known cardiovascular risk factors, including hyperglycemia/insulin resistance, obesity, atherogenic dyslipidemia, and hypertension.
- Metabolic syndrome is present if *at least three of the five* following criteria are met [42]:

1. waist circumference >40 in. (men) or 35 in. (women); note: lower thresholds are supported for South and East Asian populations
2. blood pressure >130/85 mmHg
3. fasting triglycerides (TG) >150 mg/dL
4. HDL cholesterol <40 (men) or 50 (women) mg/dL
5. fasting blood sugar >100 mg/dL

- Medical therapy for any of the above meets the respective criteria
- Metabolic syndrome increases risk for CVD by twofold [35–37], and risk of T2D fivefold [43, 44].

Prevention of Diabetes

Lifestyle Modification

- Lifestyle modification aimed at weight loss, low glycemic diet, and routine exercise are the hallmarks of diabetes prevention in the setting of metabolic syndrome.
  - In the Finnish Diabetes Prevention Study (DPS), a weight-loss plus exercise program was associated with a reduction in the incidence of diabetes by 58% compared to standard-of-care [45, 46]

- In the larger Diabetes Prevention Program, an intensive lifestyle modification program was separately compared to metformin and standard-of-care. The trial was terminated early due to overwhelming benefit. It showed that lifestyle modification reduced the risk of incident diabetes also by 58% and metformin by 31% compared to standard-of-care [47].

Metformin

- As mentioned above, metformin is effective in reducing the risk of developing diabetes among those with the metabolic syndrome
- It is controversial whether metformin truly prevents diabetes or delays the diagnosis of diabetes.

Treatment of Hyperglycemia

Treatment Targets and Initiation

- Improved glycemic control reduces the risk of microvascular complications. *The data regarding **intensive glucose** control in T2D and macrovascular complication risk is mixed* [48, 49].
- A reasonable goal for most patients is HbA1c ≤ 7.0%. Higher targets may be considered for older patients, those with multiple comorbidities, or limited life expectancy.
- For most patients, *pharmacologic therapy should be initiated at HbA1c > 7.5%.*
  - A trial of lifestyle modification should be considered for motivated patients with HbA1c 6.5–7.5%.
  - Insulin should be considered when HbA1c is far from goal.

Medications for Diabetes (Table 5-5)

Metformin
- Initial pharmacologic treatment of choice for most patients
- limits release of glucose by the liver, and reduces peripheral insulin resistance
- low risk of hypoglycemia or weight gain
- has gastrointestinal (GI) side effects and is best taken with meals
- rare side effect of lactic acidosis; risk is elevated in the setting of intravenous contrast or co-morbidities such as CKD. Hold Metformin with IV contrast.
- Contraindications: eGFR < 30 mL/min, reduced liver synthetic function

Sulfonylureas
- examples include glyburide, glimepiride, glipizide
- act as insulin secretagogues (stimulate pancreatic beta cells to secrete insulin)
- side effects of hypoglycemia, weight gain, and rash
- metabolized by liver and excreted by kidneys, so caution in liver and renal failure
- Possible increase in risk for cardiovascular events related to some agents in the class

Thiazolidinediones
- examples include rosiglitazone, pioglitazone
- peroxisome proliferator-activated receptor (PPAR)-gamma agonists
- side effects include weight gain, fluid retention, and increased risk of bone fracture
- not associated with hypoglycemia
- caution in congestive heart failure (CHF) due to fluid retention
- rosiglitazone associated with increased risk of myocardial infarction (MI)
- metabolized by liver

TABLE 5-5

APPROACH TO MEDICAL THERAPY FOR TYPE II DIABETES

INTERVENTION	EXPECTED DECREASE IN HBA1C (%)	ADVANTAGES	CONCERNS
Initial approach			
Lifestyle modifications to lose weight and increase physical activity	1–2	Effective Low cost Additional benefits	Difficult to maintain
Metformin	1–2	Low risk of hypoglycemia Low risk of weight gain Inexpensive	Lactic acidosis Avoid in renal failure GI side effects
Additional therapy			
Sulfonylureas	1–2	Inexpensive	Weight gain Hypoglycemia
Thiazolidinediones	1–2	Pio improves lipid profile	*Increased MI risk* *Avoid in CHF (wt gain, fluid retention)*
Insulin	Unlimited	No dose limit Inexpensive Improved lipid profile	Injections Hypoglycemia Weight gain Fingerstick monitoring
SGLT-2 inhibitors	0.5–1	Associated with overall *lower CV mortality, driven by lower CHF events*	Hypotension, hypovolemia, UTIs, candidal vulvovaginitis, DKA, bone fractures
Other medications			
GLP-1 agonists (aka incretins)	0.5–1	Weight loss Low risk of hypoglycemia *Lower CV mortality*	Injections GI side effects
DPP4 inhibitors	0.5–1	Once a day dosing Low risk of hypoglycemia No effect on weight	
Meglitinides	1–1.5	Short acting	Injections Take with meals
Amylin analog	0.5–1		Injections Hypoglycemia Weight loss
Alpha glucosidase inhibitors	0.5		GI side effects

Glucagon-like peptide-1 (GLP-1) agonists

- examples include exenatide, liraglutide, semaglutide
- must be given by injection once or twice a day
- bind to GLP-1 receptors to increase post-prandial insulin secretion and reduce glucagon
- **associated with lower cardiovascular mortality among those with both T2D and CVD**
- causes weight loss
- slows GI motility, and can cause nausea and vomiting
- exenatide is excreted by kidneys

Dipeptidyl protease-4 (DPP4) inhibitors

- examples include sitagliptin, saxagliptin, alogliptin, linagliptin
- block DPP4, the enzyme that breaks down GLP-1
- once daily, oral

- low risk of hypoglycemia
- no effect on weight, no GI side effects
- renal metabolism

SGLT-2 Inhibitors

- examples include canagliflozin, dapagliflozin, empagliflozin
- inhibits the action of sodium-glucose transport protein 2 (SGLT 2) in the proximal tubule, thereby reducing renal glucose reabsorption
- once daily, oral
- associated with overall **lower cardiovascular mortality in patients with concomitant T2D and CVD, primarily driven by lower CHF events**. (See "Macrovascular Complications" section below)
- associated with weight loss
- associated with hypotension/hypovolemia, UTIs, and candidal vulvovaginitis
- also reported are euglycemic diabetic ketoacidosis, cancer, bone fracture, and lower limb amputations, though this is possibly limited to canagliflozin
- metabolized by glucoronidation to an inactive metabolite and excreted in urine and feces
- Indicated for patients with estimated GFR > 45–60 mL/min/1.73 m^2

Insulin (Table 5-6)

- examples include insulin lispro, insulin regular, insulin glargine (from shortest to longest lasting formulation)
- SQ or IV
- its ability to reduce HbA1c is unlimited
- can cause severe hypoglycemia
- associated with weight gain

TABLE 5-6

INSULIN THERAPY FOR TYPE II DIABETES

INSULIN TYPE (BRAND NAME)	ROUTE	ONSET	PEAK	DURATION	USE
Rapid					
Lispro (Humalog)	SC	30 min	30–90 min	<6 h	At the same time as the meal
Aspart (Novolog)	SC	15 min	1–3 h	3–5 h	
Glulisine (Apidra)	SC	30 min	30–90 min	<6 h	
Short					
Regular (Humulin R, Novolin R)	SC	30–60 min	2–4 h	6–12 h	30–60 min before meals
Regular (Humulin R, Novolin R)	IV	15 min	15–30 min	30–60 min	
Intermediate					
NPH (Humulin N, Novolin N)	SC	1–2 h	4–14 h	10–24 h	BID or overnight
Long					
Glargine (Lantus)	SC	1 h	No peak	24 h	Daily
Detemir (Levemir)	SC	1 h	No peak	6–23 h	
Pre-mixed					
Novolog Mix 70/30 (aspart protamine/aspart)	SC	15 min	1–4 h	12–24 h	BID before mealtime
Humalog Mix 50/50 or 75/25 (lispro protamine/lispro)	SC	30 min	30 min–2 h	6–12 h	
Humulin Mix 50/50 or 70/30 (NPH/regular)	SC	30 min	2–4 h	16–24 h	

Glycemic Control and Complications

Microvascular complications

- Microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy.
- Degree of glycemic control is associated with risk of microvascular complications.
- Routine screening for these manifestations is associated with reduced morbidity.

Macrovascular complications

- In contrast to microvascular complications, macrovascular complications (coronary disease, MI, stroke) are less consistently associated with degree of glycemic control.
- Novel hypoglycemics were recently shown to reduce cardiovascular mortality in the setting of both T2D and established cardiovascular disease.
  - **SGLT2 inhibitors** work by reducing tubular reabsorption of glucose to induce glucosuria and lower serum glucose levels, and merit special mention in the reduction of macrovascular endpoints.
    - Empagliflozin and dapagliflozin have both been associated with reduced cardiovascular death, dapagliflozin with lower rates of hospitalizations for HF, and canagliflozin reduced combined cardiovascular endpoints (though not death) in patients with diabetes, despite a modest reduction in blood sugar levels [50–52].
    - Associated with a decrease in HbA1c of about 0.5%
    - In addition to weight loss, side effects of SGLT2 inhibitors include hypotension and candidal vulvovaginitis; canagliflozin in particular has been associated with increased risk of fracture and lower limb amputations compared to other agents in this class SGLT2 inhibitors are a useful adjunct in high-risk patients with manifest CVD who cannot reach their glycemic targets with conventional therapy alone, particularly in those with coexisting heart failure or CKD (eGFR > 30 mL/min/1.73 m^2).
  - **GLP1 agonists**, liraglutide and semaglutide, also showed benefit among those with cardiovascular disease [53–55]
    - Liraglutide use was associated with a reduction in cardiovascular death while semaglutide was associated with a reduction in major adverse cardiovascular events, driven by a reduction in rates of stroke, but not specifically in cardiovascular death.

Diabetes and Cardiac Risk

Treatment of Hyperlipidemia

- In the 2018 ACC/AHA Guidelines on the treatment of blood cholesterol (see section Diagnosis and Screening on Lipoprotein Disorders) patients aged 40–75 years old with LDL-C > 70 mg/dL and diabetes mellitus, with or without ASCVD, **at least a moderate-intensity statin** is recommended [56].
- In adults with diabetes mellitus and multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.
- In adults with diabetes mellitus, without ASCVD, and 10-year ASCVD risk >20%, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C by 50% or more.
- In adults older than 75 years with diabetes it may be reasonable to initiate statin therapy after a clinician-patient discussion of potential health benefits and risks.
- In adults aged 20–39 years with diabetes with high risk features, it may be reasonable to initiate statin therapy
  - High risk features include a long duration of disease (>10 years of T2D, >20 years of T1D), albuminuria, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, retinopathy, neuropathy, or ABI (<0.9)

Thiazolidinediones, CHF, and MI

- Both rosiglitazone and pioglitazone may cause or exacerbate CHF
- Meta-analyses suggest that rosiglitazone is associated with excess risk for nonfatal MI with RR of 1.43 [57]; similar findings have not been demonstrated for pioglitazone
- FDA issued a "black box" warning for MI risk for rosiglitazone in 2007
- Given the cardiovascular disease risks for thiazolidinediones, they are no longer routinely used in clinical practice

Acute Coronary Syndrome (ACS) and Glucose Control

- 2014 ACC/AHA guidelines recommend maintaining *blood sugar <180 mg/dL* for those with and without diabetes in the setting of acute myocardial infarction, while avoiding hypoglycemia.
- Given the risk of lactic acidosis from metformin use and IV contrast, metformin should be held.

Questions and Answers

Question 1:
A 59-year-old obese man with T2D, former smoker, stage 1 chronic kidney disease, hypertension, and hyperlipidemia is wondering how he can reduce his cardiovascular risk. His medications include aspirin 81 mg daily, lisinopril 20 mg daily, rosuvastatin 40 mg daily, omeprazole 20 mg daily, metformin 1000 mg twice daily, and a daily multivitamin. His laboratory tests include:

- Hemoglobin A1c 8.0%
- Total cholesterol 164 mg/dL
- HDL cholesterol 39 mg/dL
- Triglycerides 160 mg/dL
- LDL cholesterol 93 mg/dL
- Creatinine 1.1 mg/dL

His BMI is 31 kg/m^2, heart rate is 72 bpm, and blood pressure is 112/72 mmHg. He recently had a chest CT done in the emergency department to rule out a pulmonary embolism; while he was not found to have a pulmonary embolism, the chest CT read was notable for coronary artery calcifications. Which of the following is MOST ACCURATE?

A. canagliflozin will reduce his risk of cardiovascular death
B. aggressive LDL cholesterol-lowering with evolocumab is indicated
C. bariatric surgery should be pursued
D. tighter glycemic control may not reduce his cardiovascular risk
E. niacin is necessary to improve his HDL cholesterol and reduce his CVD risk

Answer 1:
Correct Answer: D.

Randomized controlled trials of intensive glycemic control and macrovascular complications have shown mixed results; as a result, intensive glycemic control is not a primary goal of reducing macrovascular risk. However, in recent trials SGLT2-inhibitors have made some headway in this regard. Empagliflozin has been shown to decrease death from cardiovascular causes, hospitalizations for heart failure, and death from any cause. Canagliflozin was shown to reduce major adverse cardiovascular events in the setting of T2D and prevalent clinical cardiovascular disease but CV death alone was not reduced. Dapagliflozin has not been shown to reduce major adverse cardiac events, but was associated with lower rates of cardiovascular death and heart failure hospitalizations. Given the patient's risk factors, it is not surprising that there is subclinical coronary atherosclerosis on chest CT, and we do not

know the burden; this alone does not establish clinically-significant CAD. As such, while further LDL cholesterol-lowering may further lower CVD risk, given the absence of clear familial hypercholesterolemia or clinical ASCVD, he is not a candidate for evolocumab. Bariatric surgery is indicated when BMI is >35 kg/m^2 in the setting of T2D. Niacin, in multiple contemporary clinical trials, has not been shown to be an efficacious strategy to lower CVD risk [50–52, 58, 59].

Questions 2 and 3:

The following vignette will be referred to for both questions 2 and 3

A 64 yo woman of European ancestry who is a never-smoker with hypertension, hyperlipidemia, and previous pregnancy complicated by gestational diabetes now presents to your clinic for routine cardiovascular care. She notes that she has been gaining weight for the past several years and is concerned about her risk of developing coronary artery disease. Her home medications include chlorthalidone 12.5 mg daily, lisinopril 20 mg daily, and aspirin 81 mg daily. In the clinic her heart rate is 68 bpm, blood pressure is 112/70, BMI is 33 kg/m^2, waist circumference of 38 in. Her laboratory results are the following:

- Hemoglobin A1c 6.1%
- Fasting Blood Sugar 110 mg/dL
- Total Cholesterol 178 mg/dL
- HDL Cholesterol 55 mg/dL
- Triglycerides 140 mg/dL
- LDL Cholesterol 123 mg/dL

Question 2

Which of the following statements is most true about the above patient?

A. The patient has the metabolic syndrome and thus her risk for CVD is elevated 10-fold
B. The patient does not have the metabolic syndrome, but does have an increased risk of CVD
C. The patient has prediabetes and thus she should be considered to have a CAD equivalent when considering her future ASCVD risk
D. The patient has both prediabetes and the metabolic syndrome, and should have her ASCVD risk calculated using the Pooled Cohort Equation prior to treatment decisions
E. The patient has neither prediabetes nor the metabolic syndrome, but should not have her ASCVD risk calculated using the Pooled Cohort Equation prior to treatment decisions

Answer 2

Correct Answer: D

The patient meets diagnostic criteria for prediabetes based off of both a fasting plasma glucose level between 100 and 120 mg/dL, and a hemoglobin A1c between 5.7 and 6.5%. She can be diagnosed with the metabolic syndrome by meeting the following three criteria: (1) waist circumference >40 in. (men) or 35 in. (women); (2) treatment for high blood pressure; (3) fasting blood sugar >100 mg/dL. The metabolic syndrome increases risk for CVD by twofold, and risk of T2D fivefold. During this clinic visit to help estimate her risk of ASCVD the clinician should calculate her risk using the Pooled Cohort Equation available online. She is a never-smoker between the ages 40–75 with well-controlled hypertension, prediabetes, on aspirin therapy. Her estimated 10-year ASCVD risk is 4.9%, and as such would not fall into a statin-benefit group.

Question 3:

Which of the following interventions if well-implemented would best lower her risk of developing diabetes in the future?

A. Initiating metformin therapy at 1000 mg twice daily
B. Enrolling the patient in an intensive lifestyle modification program
C. Initiating rosuvastatin 20 mg daily
D. Implementation of a low sodium diet

Answer 3:
Correct Answer: B

If implemented well, intensive lifestyle modification programs can have a profound effect in diabetes and pre-diabetes. As demonstrated in both the Finnish Diabetes Prevention Study (DPS) and the Diabetes Prevention Program (DPP), intensive lifestyle modification reduced the incidence of diabetes 58%. The DPP was in fact stopped early because of overwhelming benefit. It showed that lifestyle modification reduced the risk of incident diabetes also by 58% and metformin by 31% compared to standard-of-care. Metformin initiation would also be a reasonable choice in this patient. As noted above, the patient would not fall into one of the statin benefit groups (see section Diagnosis and Screening on Lipoprotein Disorders), and indeed statins may increase risk of progression to diabetes in patients with prediabetes. Despite this, statins are not contraindicated in this population. Implementation of a low sodium diet is likely to help with hypertension and overall ASCVD risk, but will not likely affect her risk of progression to diabetes.

LIPOPROTEIN DISORDERS

Disorders of serum lipid and lipoproteins are estimated to account for approximately 50% of population-attributable risk for myocardial infarction (MI) [60, 61]. Randomized controlled trial (RCT) data demonstrate that treating elevated levels of low density lipoprotein cholesterol (LDL-C) results in reductions in cardiovascular events and death [62–64]. Despite a strong inverse correlation between high density lipoprotein cholesterol (HDL-C) levels and CVD risk, randomized clinical trials (RCTs) aimed at increasing steady-state HDL-C levels have failed to demonstrate favorable effects on cardiovascular outcomes.

Overview of Lipoprotein Metabolism

- Three major types of lipids circulate in the serum:
  - Cholesterol- essential component of cell membranes and substrate for synthesis of steroid hormones and bile acids
  - Triglycerides (TG)- macromolecules consisting of glycerol backbone connected to three fatty acids (FA)
  - Phospholipids (PL)- important constituents of cell membranes
- Lipoproteins are water-soluble particles that carry lipids and associated proteins throughout the bloodstream. Circulating lipoproteins are comprised of a hydrophobic core with cholesterol ester (CE) and TGs and an outer shell enriched in polar lipids including free cholesterol and phospholipids and free cholesterol (FE). In addition, each lipoprotein harbors a distinctive repertoire of apolipoproteins that dictates its functional properties.
- Lipoproteins are classified according to their density in plasma (Table 5-7).
  - Atherogenic lipoproteins, such as chylomicrons, chylomicron remnants, VLDL, IDL, LDL, and lipoprotein(a), are characterized by harboring apoB. ApoB can be directly measured or estimated from the non-HDL-C concentration (i.e., difference between total cholesterol and HDL-C).

TABLE 5-7

PLASMA LIPOPROTEINS

LIPOPROTEIN	PRIMARY LIPID COMPONENT
Chylomicron (CM)	TG
CM remnant	TG
Very low density lipoprotein (VLDL)	TG
Intermediate density lipoprotein (IDL)	TG, CE
LDL	CE
High density lipoprotein (HDL)	CE, TG

- Lipoprotein(a), or Lp(a), is a highly heritable, LDL-like lipoprotein that confers a modest increased risk of CAD independent of LDL-C
  - Lp(a) contains the Apo(a) apolipoprotein, which has structural homology to plasminogen but lacks any fibrinolytic activity
  - Apo(a) may interfere with plasminogen activity and contribute to a pro-thrombotic state
  - **Routine measurement of Lp(a) is not recommended.** Yield may be increased in the setting of a *personal or family history of premature CAD*. While *statins* do not lower Lp(a), conferred risk may be offset by aggressive LDL-C-lowering [65, 66].
- Two important pathways coordinate lipoprotein transport:
  - Intestinal (or prandial) pathway (Fig. 5-8):
    - Coordinates transfer of dietary TG to the liver and peripheral tissues
    - Dietary TG in intestinal epithelial cells are packaged with ApoB and a small amount of cholesterol to form chylomicron (CM) lipoproteins
    - CM are secreted into the circulation and acquire ApoC and E from HDL
    - TG within CM undergo hydrolysis by lipoprotein lipase (LPL) on endothelial cells; released free fatty acids (FFA) are taken up for energy storage
  - Hepatic (or fasting) pathway (Fig. 5-9):
    - Coordinates the transport of TG and cholesterol between the liver and target peripheral tissues
    - Hepatocytes package TG with ApoB to form VLDL
    - In the circulation, VLDL interacts with HDL to: (1) acquire additional lipoproteins, and (2) exchange TG for CE

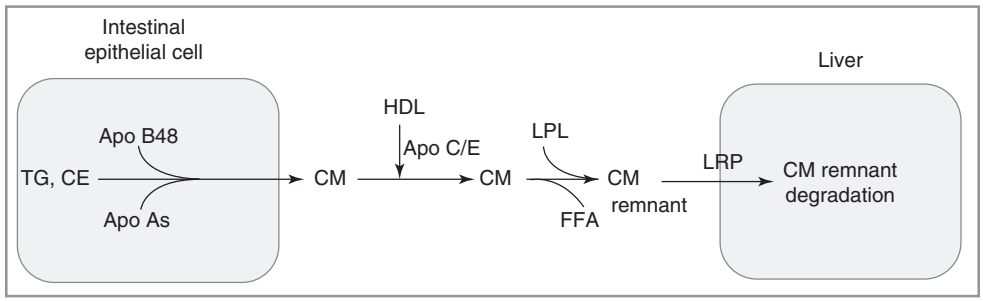


FIGURE 5-8

Schematic of intestinal pathway. Chylomicrons (CM) are assembled in intestinal epithelial cells and secreted into the circulation, where they undergo lipolysis by lipoprotein lipase (LPL). CM-remnants are taken up by the liver. *LRP* lipoprotein receptor-related protein

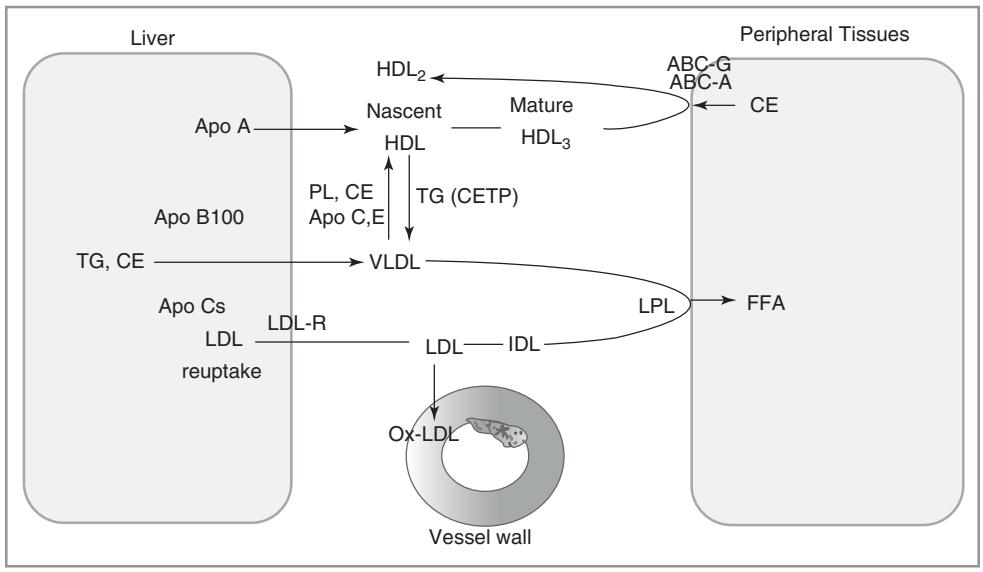


FIGURE 5-9

Schematic of hepatic pathway. TG-rich VLDL are assembled in the liver and secreted into the circulation. Cholesteryl ester transfer protein (CETP) facilitates transfer of TG from VLDL to HDL in exchange for cholesterol. VLDL is hydrolyzed by LPL to release FFA that are taken up by peripheral tissues (fat, muscle). LDL generated from LPL action can enter the vessel wall, where its oxidation and uptake by macrophages leads to foam cell formation, a key step in atherogenesis. Nascent HDL secreted from the liver play an important in reverse cholesterol transport

- VLDL TGs undergo lipolysis by LPL to produce FFA
  - Hydrolysis yields IDL, which undergoes further hydrolysis by hepatic lipase to form LDL, the main courier of FC and CE
- LDL is taken up by the liver, a process mediated by the LDL receptor (LDL-R)
- LDL can also be taken up by macrophages in arterial vessel walls leading to foam cell formation, a key step in atherogenesis

Lipoproteins Disorders and CAD Risk

- Several lipid and lipoprotein variables have been associated with an increased risk of CAD [64, 67–74]:
  - Elevated total cholesterol (TC) and LDL cholesterol (LDL-C)
  - Low HDL-C and high TG
  - Elevated non-HDL cholesterol (a measure of the total burden of ApoB-containing atherogenic lipopoprotein particles)
  - Apo B lipoprotein levels, and ApoB/ApoAI ratio
  - Elevated Lp(a)
  - Small, dense LDL particles
- A continuous log-linear relationship exists between LDL-C and CAD risk
  - a decrease of 1 mmol/L (~40 mg/dL) in LDL-C results in a 21% decrease in CHD relative risk [75]
  - a given change in LDL-C produces the same change in relative risk of CHD at virtually any baseline level of LDL-C
- Non-HDL-C and apoB are highly correlated with LDL-C but also include other apoB-containing lipoproteins, such as triglyceride-rich lipoproteins and Lp(a). ApoB is associated with modestly greater CAD risk compared to non-HDL-C and LDL-C [74].
- To-date several randomized controlled trials and genetic epidemiology studies indicate that HDL-C concentrations are likely not causally associated with CAD risk [76–80].
- Recent genetic epidemiology studies indicate that TG-rich lipoproteins may be causally associated with CAD [81].

Diagnosis and Screening

- The Friedewald formula is used to calculate LDL-C, because direct measurement of LDL-C is time-consuming, costly, and often imprecise [82]: LDL-C = TC – (HDL-C + TG/5)
- The LDL-C calculated from the Friedewald formula is inaccurate at higher TG levels, and *direct measurement of LDL-C should be considered if TG > 400 mg/dL*.
- Understanding the limitations of the Friedewald formula in assuming a triglyceride:HDL ratio of 5:1 in all patients, newer formulae such as the Martin-Hopkins formula have been developed, which can be more accurate in LDL-C estimation when TG are elevated or when LDL-C is very low. The calculator can be found online at https://www.hopkins-medicine.org/apps/all-apps/ldl-cholesterol-calculator [83]
- Significant elevations in LDL-C (>190 mg/dL) may indicate the potential presence of familial hypercholesterolemia (autosomal dominant genetic condition primarily due to mutations in *LDLR*, *APOB*, or *PCSK9*; prevalence 1:250 in the general population and 1:50 among individuals with LDL-C > 190 mg/dL), manifested in markedly elevated LDL-C and premature CHD risk.

Management of Lipoprotein Disorders

Hydroxymethylglutaryl-Coenzyme A Reductase Inhibitors (Statins)

- Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in sterol synthesis
- Statins increase expression of LDL-R and decrease CE formation, leading to enhanced LDL-C clearance from plasma and reduced VLDL production
- **Statins are the drugs of choice for reducing LDL-C (20–55% reduction) and thus for reduction of ASCVD risk**
- Statins also modestly decrease TG (5–30%) and increase HDL-C (2–10%)
- Indications for statin therapy are discussed at length in the following sections
- In patients >75 years old, statins are efficacious, but statin intensity may be reduced where appropriate
- Statins are safe: mild elevations in AST/ALT occur in 3% but drug-induced liver injury is very rare and myopathy is 0.2% in blinded clinical trials [62]. The difference in myopathy between statin and placebo in blinded clinical trials is not significant [84].
- The risk of myopathy is significantly higher with 80 mg of simvastatin and doses higher than 40 mg of simvastatin are not recommended
- Lovastatin, simvastatin, and atorvastatin are metabolized by CYP 3A4 and should be used with caution with other drugs that are metabolized using the same pathway (such as macrolides, antifungals, cyclosporine, verapamil, amlodipine, ranolazine, or large quantities of grapefruit juice)
- Statins are contraindicated in pregnancy (Class X for known teratogenic effects), and other alternatives such as bile acid sequestrants (Class B) should be considered where necessary during pregnancy and breast-feeding (Table 5-8)

Fibrates

- Fibrates activate peroxisome proliferator-activated receptor alpha (PPARα) which increases apoA-I and represses apoB and VLDL production
- Lower TG 20–35% and increase HDL-C by 6–18% with modest effect on LDL-C (~20% reduction)
- Drugs of choice for severe hypertriglyceridemia
- Helsinki Heart Study and VA-HIT trials showed fibrate monotherapy reduces CV events [85, 86]

TABLE 5-8

STATINS OF HIGH-, MODERATE-, AND LOW-INTENSITY AS DEFINED BY THE 2018 ACC/AHA GUIDELINES

HIGH-INTENSITY	MODERATE-INTENSITY	LOW-INTENSITY
Daily dose decreases LDL-C by ≥50%	*Daily dose decreases LDL-C by 30–50%*	*Daily administration decreases LDL-C by <30%*
Atorvastatin (40 mg[a]) 80 mg **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg**[b] **Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	Simvastatin 10 mg **Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

Statins in **boldface type** demonstrated reduction in major adverse cardiovascular events in randomized controlled trials (RCTs)

Source: 2018 AHA Guideline on the Management of Blood Cholesterol

[a]Atorvastatin 40 mg was evaluated in a single RCT, IDEAL (Incremental Decrease through Aggressive Lipid Lowering), in patients unable to tolerate atorvastatin 80 mg

[b]Simvastatin 80 mg has been evaluated in RCTs, but dose is not recommended in clinical practice due to high risk of myopathy, including rhabdomyolysis

- However, the FIELD and ACCORD showed no benefit, and as such, in the absence of marked hypertriglyceridemia (>500 mg/dL) the value of fibrates remains less clear
- Gemfibrozil can inhibit glucuronidation and elimination of statins, thereby significantly increasing the risk of statin-myotoxicity

Niacin

- Niacin has multiple effects including suppression of lipolysis, reduced hepatic synthesis of TG and VLDL secretion, increased apoB degradation, and decreased catabolism of HDL
- Most potent commercially-available HDL-C-raising agent (10–35%) that also lowers TG (20–30%) and LDL-C (10–25%)
- Niacin lowers Lp(a) (10–20%) but it is currently unclear if niacin lowers CAD risk in the setting of elevated Lp(a).
- Side effects include cutaneous flushing, hyperuricemia, transaminitis, and hyperglycemia

Two recent trials demonstrated that the addition of niacin to statins did not further reduce cardiovascular risk; thus, niacin is not routinely recommended for CVD risk reduction [76, 78].

Bile Acid Sequestrants

- Interrupt reabsorption of cholesterol-containing bile acids
- Mainly used as an adjunctive therapy in patients with severe elevations in LDL-C, or in the setting of **pregnancy** to manage hyperlipidemia
- Modest decreases in LDL-C (15–30%) and small increases in HDL-C (5–15%)
- Frequent GI side effects and occasionally results in *hypertriglyceridemia*

Cholesterol Absorption Inhibitors (Ezetimibe)

- Inhibits intestinal cholesterol absorption via cholesterol transport interference
- Addition of ezetimibe to statins decreases LDL-C by an additional 25–30%, and modestly decreases cardiovascular risk (by 7%) in the setting of secondary prevention. Despite results from the IMPROVE-IT study, it is currently only FDA approved for the management of familial hypercholesterolemia [87]. However, in the 2018 ACC/AHA cholesterol guidelines, its use is supported for secondary prevention when LDL-C is not at a suitable level on maximally tolerated statin and dietary changes.

Proprotein convertase subtilsin-kexin type 9 (PCSK9) Inhibitors

- PCSK9 promotes the degradation of LDL-R; inhibition promotes LDL-R availability at the hepatocyte surfaces to promote LDL-C clearance from the plasma
- Two PCSK9 monoclonal antibodies, alirocumab and evolocumab, have been shown to reduce LDL-C and reduce ASCVD events [88, 89].
- Both alirocumab and evolocumab are associated with, on average, a 60% reduction in LDL-C, even in those already on statin therapy.
- The FOURIER trial in 27,564 patients with established CVD showed that administration of evolocumab on a background of statin therapy resulted in fewer cardiovascular events, although no reduction in cardiovascular or all-cause mortality was detected, perhaps due to the study's limited follow-up period (median 2.2 years).
- The ODYSSEY Outcomes trial with alirocumab in patients with recent acute coronary syndrome similarly showed a reduction in major cardiovascular events after a median follow-up of 2.8 years; in a secondary analysis, the degree of risk reduction varied according to pre-therapy LDL-C level.
- They are administered as injectable medications once every 2–4 weeks
- Generally well-tolerated with infrequent adverse effects, which include injection site reactions and muscle-related side-effects.
- PCSK9 inhibitors are recommended for:
  - Primary prevention in familial hypercholesterolemia. If LDL-C remains above 100 mg/dL in spite of maximal statin and ezetimibe therapy, PCSK9 inhibitors may be considered.
  - Secondary prevention for "very high-risk" ASCVD with LDL-C > 70 mg/dL despite max-tolerated diet, statin, and ezetimibe

■ Furthermore, the ACC/AHA includes a value statement regarding PCSK9 inhibitors, acknowledging that at 2018 prices, their use is associated with low economic value (>$150,000 per quality-adjusted life-year), and should thus be restricted to very high risk individuals at the present time (Table 5-9).

TABLE 5-9

PRIMARY LIPID-MODIFYING DRUG CLASSES

DRUG CLASS	METABOLIC EFFECTS	CLINICAL CONSIDERATIONS
Statins	↓LDL-C 20–55% ↑HDL-C 2–10%[a] ↓TG 5–30%	■ ↓CV events, CHD deaths, need for PCI, CVA, total mortality ■ Liver and muscle toxicity (monitor CK, LFTs) ■ Potential drug interactions between some statins[b] and CYP450 3A4 inhibitors (macrolides, antifungals, cyclosporine, grapefruit juice) ■ Use with caution with fibrates (avoid gemfibrozil) and niacin ■ Avoid simvastatin at 80mg (ok to continue if tolerated > 1 year) ■ Absolute contraindications: active or chronic liver disease ■ Relative contraindications: concomitant use of some drugs
Fibrates: Gemfibrozil Fenofibrate	↓TG 20–35% ↑HDL-C 6–20% ↓TC/LDL-C 20–25%[c]	■ Reduced CV events (monotherapy) in 1^0 and 2^0 prevention ■ No benefit observed in statin-treated DM patients with dyslipidemia ■ GI side effects, transaminitis, muscle injury, elevation in creatine (not related to reduction in GFR) ■ Absolute contraindications: severe renal/hepatic disease ■ Relative contraindications: statins (avoid gemfibrozil)
Nicotinic Acid: Multiple OTCs Prescription: Slo-Niacin Niaspan	↓TG 20–30% ↑HDL-C 10–35% ↓LDL-C 10–20%	■ **Recent trial data show no benefit** in statin-treated patients with well controlled LDL-C and persistent low HDL-C ■ Frequent side effects: cutaneous flushing, hyperuricemia, hypertriglyceridemia, hepatotoxicity, gastritis ■ Contraindications: hepatic disease, severe gout
Bile acid sequestrants: Cholestyramine Colestipol Colesevam	↓LDL-C 15–25%	■ Mainly used as adjunctive therapy for LDL-C lowering ■ Frequent GI side effects and may increase TG ■ Many potential drug interactions ■ Interferes with absorption of other drugs (administer 1 h after or 3 h before other medications) ■ Absolute contraindications: TG > 400 mg/dL ■ Relative contraindications: TG > 200 mg/dL
Cholesterol Absorption Inhibitor: **Ezetimibe**	↓LDL-C 10–20% ↓LDL-C additional 25% with statin	■ Used primarily as adjunctive therapy with statin for LDL-C lowering ■ No trial data to support incremental clinical benefit over statin alone ■ Rarely causes myopathy
PCSK9 inhibitors	↓LDL-C by 60%	■ Injectable medication taken every 2–4 weeks ■ Generally very well tolerated with injection site reactions being the primary adverse effect ■ Have been shown to reduce ASCVD events on a background of statin therapy ■ Should be considered in high risk patients who have not met therapy goals after a statin and ezetimibe have been initiated, or in statin-intolerant patients.

[a]Less consistent than LDL effects
[b]Lovastatin, simvastatin > atorvastatin
[c]May increase LDL-C in patients with elevated TGs ("beta-shift")

Core Concepts from 2018 ACC/AHA Guidelines

The recently published 2018 ACC/AHA Guideline on the Management of Blood Cholesterol build upon an earlier version from 2013, which introduced the model of tailoring lipid-lowering therapy to global cardiovascular risk, rather than steady-state LDL-C levels. Emphasis is placed on lifestyle modification, and in addition to more carefully refined risk-categories, 'risk-enhancing factors' are noted for patients at intermediate risk of ASCVD events.

Moderate or high-intensity statin therapy is recommended for the following four groups, using the ASCVD Risk Score (ACC/AHA Pooled Cohort Equations) for quantitative risk assessment:

1. **Clinical evidence of ASCVD**
   - *Recommendation: High-intensity statin for >50% LDL-C reduction*
2. **Adults 40–75 years old with diabetes mellitus and LDL-C ≥ 70 mg/dL**
   - *Recommendation: Moderate-intensity statin, consider high-intensity if CVD risk ≥7.5%*
3. **Adults 40–75 years old with CVD risk score ≥7.5% and LDL-C 70–189 mg/dL**
   - *Recommendation: Moderate-intensity statin following risk discussion * * see below*
4. **Severe hypercholesterolemia with LDL-C ≥ 190 mg/dL**
   - *Recommendation: High-intensity statin, no risk assessment needed*

Additionally, the new guidelines introduce a **very high-risk category**—**those patients with multiple ASCVD events or one major ASCVD event and multiple risk factors**. In this group the addition of a non-statin medication to reduce the LDL-C < 70 is recommended. If the LDL-C remains elevated on a high intensity statin + ezetimibe, then a PCSK9i is reasonable, though the long term safety (greater than 3 years) has yet to be evaluated and cost-effectiveness may be a concern.

5. **Very High-Risk ASCVD:**
   - *Recommendation: High-intensity statin + non-statin therapy for those whose LDL-C remains above 70 mg/dL.*

Further Refining Risk

The guidelines emphasize that the purpose of risk calculation is not to mandate statin therapy, but rather to delineate groups in which statin initiation may be beneficial, thereby fostering shared decision-making between patient and clinician. A common clinical quandary involves risk stratification in borderline and intermediate-risk adults without clinical CVD, diabetes, or severe hypercholesterolemia. Of note, the Pooled Cohort Equations are best validated in non-Hispanic black and white populations, and thus have generated some controversy for overestimating risk in other demographics. To refine personalized risk prediction, the guidelines suggest incorporating information about other 'risk-enhancing factors' in making the decision to initiate or intensify statin therapy.

- In patients 40–75 years old **without diabetes and with ASCVD Risk of 7.5–19.9%** (intermediate risk), statins are reasonable and the presence of ***risk enhancing factors*** **(Table 5-1) favor statin initiation**
  - In the above group, with intermediate risk (ASCVD 7.5–19.9%) and LDL-C levels ≥70–189 mg/dL, if the decision to about statin therapy remains uncertain, the updated guidelines recommend consideration of **Coronary Artery Calcium (CAC) Scoring** to refine risk.
    - If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.

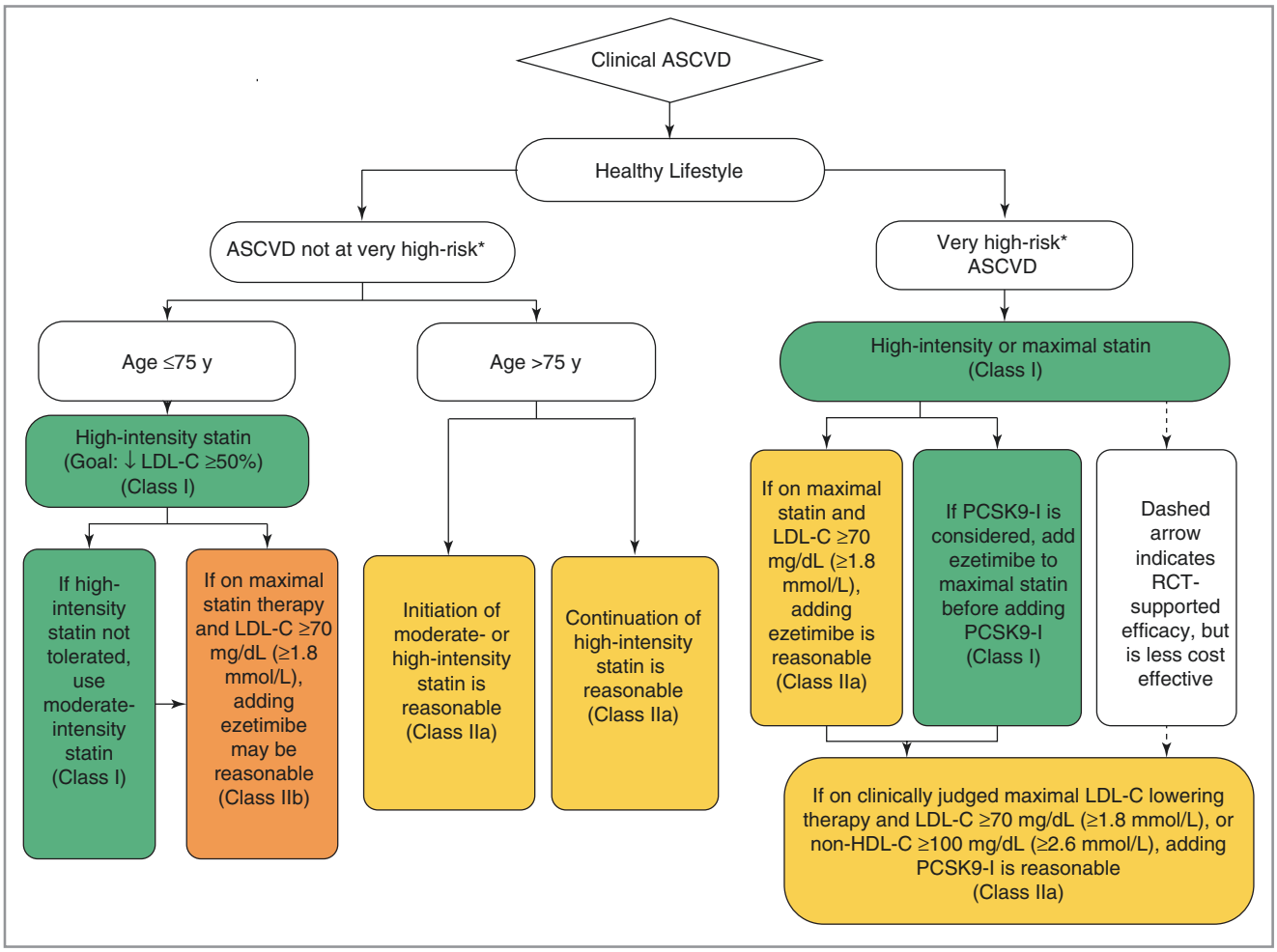


FIGURE 5-10

Summary of 2018 ACC/AHA guidelines for management of hyperlipidemia. Management strategy emphasizes atherosclerotic cardiovascular disease (ASCVD) risk assessment and treatment with the appropriate intensity statin for risk reduction (used with permission from [56])

- A CAC score of 1–99 favors statin therapy, especially in those ≥55 years of age. For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion (Fig. 5-10).

Management of Genetic Dyslipidemias

Familial Hypercholesterolemia (FH)

- Autosomal dominant disorder due to mutations in the LDL-R gene (*LDLR*) primarily (also, *APOB* and *PCSK9*); very rarely autosomal recessive form with mutations in *LDLRAP1*
- Heterozygous form (prevalence 1 in 250 people) results in markedly elevated LDL-C (often 190–350 mg/dL); however, only ~1 in 50 with LDL-C > 190 mg/dL have a familial hypercholesterolemia mutation.
- Homozygous form (prevalence 1 in 1.1 million) results in LDL-C in 400–1000 mg/dL range; *premature aortic stenosis* may be observed.
- *Tendinous xanthoma, corneal arcus senilis* may be present
- Premature CAD is common in the ***third decade in men and in the fourth decade in women***

- LDL-C-lowering therapy initiated in teenage years with statin (first line), bile acid sequestrant, or multi-drug regimen
- Homozygous FH patients often need plasma apheresis
- Family (first-degree relatives minimally) testing of at least fasting lipids indicated

Familial Defective apolipoprotein B (FDB)

- Autosomal dominant disorder due to mutation in *APOB* gene (prevalence of 1 in 1000). The phenotype is similar to familial hypercholesterolemia but with less severely elevated LDL-C or CHD risk.

Familial Chylomicronemia Syndrome

- Rare condition with markedly elevated TG due to mutations in *LPL*, or rarely *APOC2* (autosomal recessive).
- Affected individuals carry a markedly elevated risk for *pancreatitis*.
- Pharmacotherapy has limited efficacy and strict dietary therapy can be highly effective.

Genetic Disorders Affecting HDL

- Hypoalphalipoprotenemia- Low HDL-C levels due to mutations of *APOA1*
- Tangier's Disease- Low HDL-C levels due to *ABCA1* mutations
- Lecithin cholesterolacyl transferase (LCAT) Deficiency- Absent LCAT activity leads to decreased CE formation in circulating HDL particles and low HDL-C
- CETP Deficiency- Absence of CETP leads to accumulation of cholesterol in HDL, leading to high HDL-C levels.
- Rare genetic mutations in *SCARB1* leading to elevated HDL-C may increase risk for CAD [90]

Questions and Answers

Question 1

A 32 y/o female is referred to your office for consultation after a recent abnormal fasting lipid panel. She is healthy and her family history is notable for hyperlipidemia and premature CHD in her father, who suffered an MI in his 30s. She has two children and subsequently had a hysterectomy for adenomyosis. A screening fasting lipid panel showed the following:

Total cholesterol—287 mg/dL	Triglycerides—90 mg/dL
HDL-C—55 mg/dL	LDL-C—214 mg/dL

In clinic, her BP is 118/67 mmHg, HR is 66 bpm, and BMI is 22 kg/m^2. She was noted to have a nodular, mobile 0.5 cm mass over the right Achilles tendon. The ECG was within normal limits. The next best step in her treatment is to:

A. Advise her to undertake therapeutic lifestyle modifications and defer drug therapy since statins are not safe in women of childbearing age
B. Calculate her 10-year ASCVD risk and start a statin if she is classified as high risk
C. Start a statin
D. Start ezetimibe
E. Start colesevelam

Answer 1:

Correct Answer: C.

This patient likely has heterozygous familial hypercholesterolemia. Key features include the markedly elevated LDL-C (>190 mg/dL), tendinous xanthoma, and family history of premature CHD. The presence of LDL-C > 190 mg/dL establishes statin candidacy. Patients with FH are at a risk for premature CHD and should be treated with LDL-C-lowering therapy. When LDL-C is >190 mg/dL, there is no role of 10-year ASCVD risk estimation to establish statin candidacy. Concurrent therapeutic lifestyle modifications are recommended but given the evidence of FH, statins should be recommended as well. Ezetimibe lowers LDL-C and can be used as adjunctive therapy for FH but is not a first-line medication. Colesevelam is a bile acid sequestrant that can lower LDL-C in the setting of FH; it may be used in pregnancy (category B) when lipid-lowering is required. Since this patient previously had a hysterectomy, there is no risk for potential teratogenicity

from statins. If she were to continue to have an LDL-C level >100 mg/dL in spite of maximal statin and ezetimibe therapy, PCSK9 inhibitors should be considered.

Question 2:
A 59 y/o Asian American overweight man was hospitalized 4 weeks ago for a myocardial infarction. He presented with acute shortness of breath and was noted to have an EKG consistent with an inferior ST-elevation myocardial infarction. Emergent coronary angiography demonstrated a 98% mid RCA lesion which was revascularized percutaneously with a drug-eluting stent. He was newly diagnosed with diabetes mellitus and hypertension. His fasting lipids during his hospitalization were:

Total cholesterol—214 mg/dL	Triglycerides—202 mg/dL
HDL-C—32 mg/dL	LDL-C—142 mg/dL

The rest of his hospitalization course was unremarkable. You review his discharge medicines, which include atorvastatin 80 mg daily. Your patient is concerned that his "good cholesterol" is low and wonders how it should be treated. What is your recommendation?

A. Recommend dietary and physical activity modification, and weight loss
B. Tell him that "good cholesterol" is a misnomer and should be ignored
C. Start niacin
D. Start alirocumab
E. Check lipoprotein(a) concentrations

Answer 2
Correct Answer: A.

HDL-C is a non-causal risk factor associated with ASCVD risk. Nevertheless, given the several negative randomized clinical trials assessing the clinical efficacy of HDL-C-raising pharmacotherapies, they (including niacin) are not currently recommended for ASCVD risk-reduction through HDL-C-lowering. The term "good cholesterol" connotes that it is a causal risk factor and should be a therapeutic target; the data indicate that it is not a suitable therapeutic target, but it is still helpful as a clinical risk predictor. Diet, physical activity, metabolic syndrome, and weight are associated with HDL-C and are likely the correlated causal features influencing ASCVD risk. Thus, therapy should focus on non-pharmacological lifestyle strategies to reduce ASCVD risk, particularly with a goal for weight loss. Without knowing LDL-C levels on atorvastatin 80 mg daily, it is not currently clear whether alirocumab, a PCSK9 inhibitor, is necessary. Lipoprotein(a) is a heritable independent risk factor for ASCVD; trials to assess the clinical efficacy of lipoprotein(a)-lowering are ongoing.

Question 3:
A 49 y/o African American woman with hypertension (on hydrochlorothiazide) and hyperlipidemia comes to your office because she isn't sure whether she should take a statin but she clearly expresses her preference to avoid medicines if possible because she has a hard time taking daily medications. Her medical history is also notable for cholelithiasis, hypothyroidism, and gastroesophageal reflux disease. Her father died of a myocardial infarction at 63 years old and her mother currently has Alzheimer's disease. Neither of her younger brothers have notable medical issues. Her vital signs are notable for heart rate 70 bpm, blood pressure 126/80 mmHg, and BMI 25. Her lipids show:

Total cholesterol—280 mg/dL	Triglycerides—160 mg/dL
HDL-C—56 mg/dL	LDL-C—192 mg/dL

What do you recommend next?

A. Defer a statin because her 10-year ASCVD risk is estimated to be low (3.9%)
B. Start atorvastatin 20 mg daily
C. Start ezetimibe 10 mg daily
D. Check TSH
E. Order a non-contrast cardiac CT for coronary artery calcification

Answer 3:
Correct Answer: D.

Untreated hypothyroidism is a reversible cause of hyperlipidemia. The question stem indicates the patient may be inadvertently missing her thyroid hormone replacement medication and is at risk for hypothyroidism-induced hyperlipidemia. Treatment of hypothyroidism-induced hyperlipidemia is associated with an increased risk of myalgia. Thus TSH should be checked and euthyroidism should be confirmed (or established) before assessment of statin candidacy in this setting. When hypothyroidism is corrected, lipids are often improved necessitating re-evaluation of statin candidacy.

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CHAPTER 6

AKL C. FAHED AND CLAUDIA U. CHAE

Stable Ischemic Heart Disease

CHAPTER OUTLINE

ABBREVIATIONS

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndromes
AHA	American Heart Association
ARB	Angiotensin receptor blockers
BMS	Bare-Metal Stent
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
CCB	Calcium channel blockers
CCS	Canadian Cardiovascular Society
CCTA	Coronary computed tomography angiography
DAPT	Dual Antiplatelet Therapy
DES	Drug-Eluting Stent
ECG	Electrocardiogram
EBCT	Electron beam computed tomography
FFR	Fractional flow reserve
HeFH	Heterozygous Familial Hypercholesterolemia
HCTZ	Hydrochlorothiazide
iFR	Instantaneous wave-free ratio
IHD	Ischemic Heart Disease
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LBBB	Left bundle branch block
LM	Left main artery
LV	Left ventricle
MI	Myocardial infarction
MRI	Magnetic resonance imaging
OCT	Optical coherence tomography
OMT	Optimal Medical Therapy
PCI	Percutaneous coronary intervention
SIHD	Stable Ischemic Heart Disease
SPECT	Single photon emission computed tomography
T2D	Type-2 diabetes
WPW	Wolff–Parkinson–White

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EPIDEMIOLOGY

- Ischemic heart disease is the leading cause of death and is on the rise worldwide according to the Global Burden of Disease Study [1].
  - In the US, ischemic heart disease remains the leading cause of death [2], accounting to one in seven deaths and killing over 366,800 people a year [3].
  - Advances in prevention and treatment resulted in a reduction of age-adjusted mortality from ischemic heart disease by >50% between 1980 and 2000 [4]. The year-by-year reduction continues until 2013 [3].
  - The prevalence of coronary artery disease (CAD) in U.S. adults ≥20 years of age is 6.2%. It is higher for men (7.6%) compared to women (5%) [5].
- Every year in the U.S., ~660,000 people will be hospitalized for myocardial infarction (MI) or die from ischemic heart disease [5].
  - People who survive an MI have a 1.5- to 15-fold increase in morbidity or mortality, including recurrent MI, sudden death, angina pectoris, heart failure, and stroke, compared to the general population [5].
- The prevalence of diagnosed CAD is likely increasing in recent years due to the advent of more sensitive tests such as high-sensitivity troponin (hs-Tn) and CT angiography (CTA).
- Prognostic assessment and risk stratification play critical roles in the management of patients with stable ischemic heart disease (SIHD).
  - It is important to select patients who may benefit from revascularization, in contrast to those in whom medical therapy alone is indicated.
- The presence of conventional cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, family history of premature CAD, smoking), as well as obesity and sedentary lifestyle, can adversely influence prognosis in patients with SIHD.
  - Interventions to improve these risk factors can positively influence outcomes in these patients.
- The strongest predictor of survival in patients with SIHD is left ventricular (LV) systolic function, followed by the distribution and severity of coronary artery stenoses [6].
  - Left ventricular ejection fraction (LVEF) <35% is associated with annual mortality rate >3% [7].
  - Left main (LM) disease, three-vessel disease, and/or proximal left anterior descending (LAD) disease are predictors of poor outcome and increase the risk of ischemic events [8].

PATHOPHYSIOLOGY

- Atherogenesis occurs due to microscopic injury to the endothelial lining of the intima, recruitment of inflammatory cells, and accumulation of lipids in the coronary artery wall beneath the intima [9, 10].
  - The earliest macroscopically visible lesion is called a fatty streak.
  - The atherosclerotic plaque is made of a fibrous cap and a lipid rich core.
- Initially, plaque extends eccentrically and outward without significantly compromising luminal diameter (Fig. 6-1). This stage of atherosclerosis, described by Glagov as "positive arterial remodeling, is clinically silent and may not be detectable by stress testing or angiography. Luminal area is typically unaffected by plaque growth until the stenosis exceeds 40%.

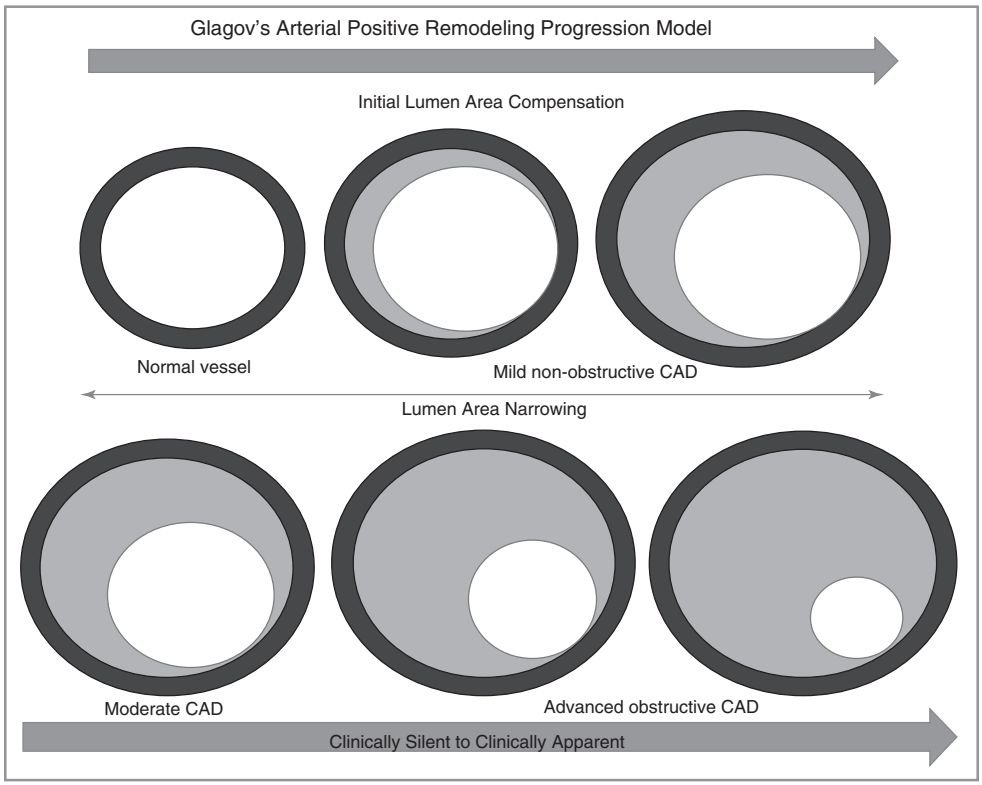

FIGURE 6-1

Progression of CAD and arterial remodeling (Glagov's arterial positive progression model)

- As the lipid rich core continues to enlarge, encroachment of the atherosclerotic plaque into the lumen ("negative arterial remodeling") can eventually result in hemodynamic obstruction and angina.

■ Increased local inflammation, due to proteinases secreted by activated leukocytes that degrade the extracellular matrix and pro-inflammatory cytokines that limit the synthesis of new collagen, can result in a thin fibrous cap that is susceptible to rupture [11].

- When a plaque ruptures, blood comes in contact with tissue factor and results in platelet aggregation and activation of the coagulation cascade, leading to thrombus formation.
- If the thrombus completely occludes the lumen of the coronary artery, downstream blood flow is impeded and a myocardial infarction occurs.
- The life history of an atheroma and the role of inflammation in the development of stable vs. unstable plaque is highlighted in Fig. 6-2.

■ Cardiac ischemia occurs when myocardial oxygen demand exceeds supply.

- Cardiac ischemia can cause either an acute coronary syndrome (ACS) (ST elevation MI, Non-ST elevation MI, or unstable angina) or chronic stable angina.
  - ■ A sudden reduction in myocardial oxygen supply caused by atherosclerotic plaque rupture or erosion and thrombosis is usually the mechanism of ACS. The degree of stenosis from these plaques can be less than 50%.
  - ■ In contrast, an increase in myocardial oxygen demand in the setting of inadequate coronary perfusion and limited ability to increase myocardial oxygen supply is usually the mechanism of ischemia in chronic stable CAD.

■ Ischemia-induced sympathetic activation can exacerbate the severity of myocardial ischemia by further increasing myocardial oxygen consumption and coronary vasoconstriction.

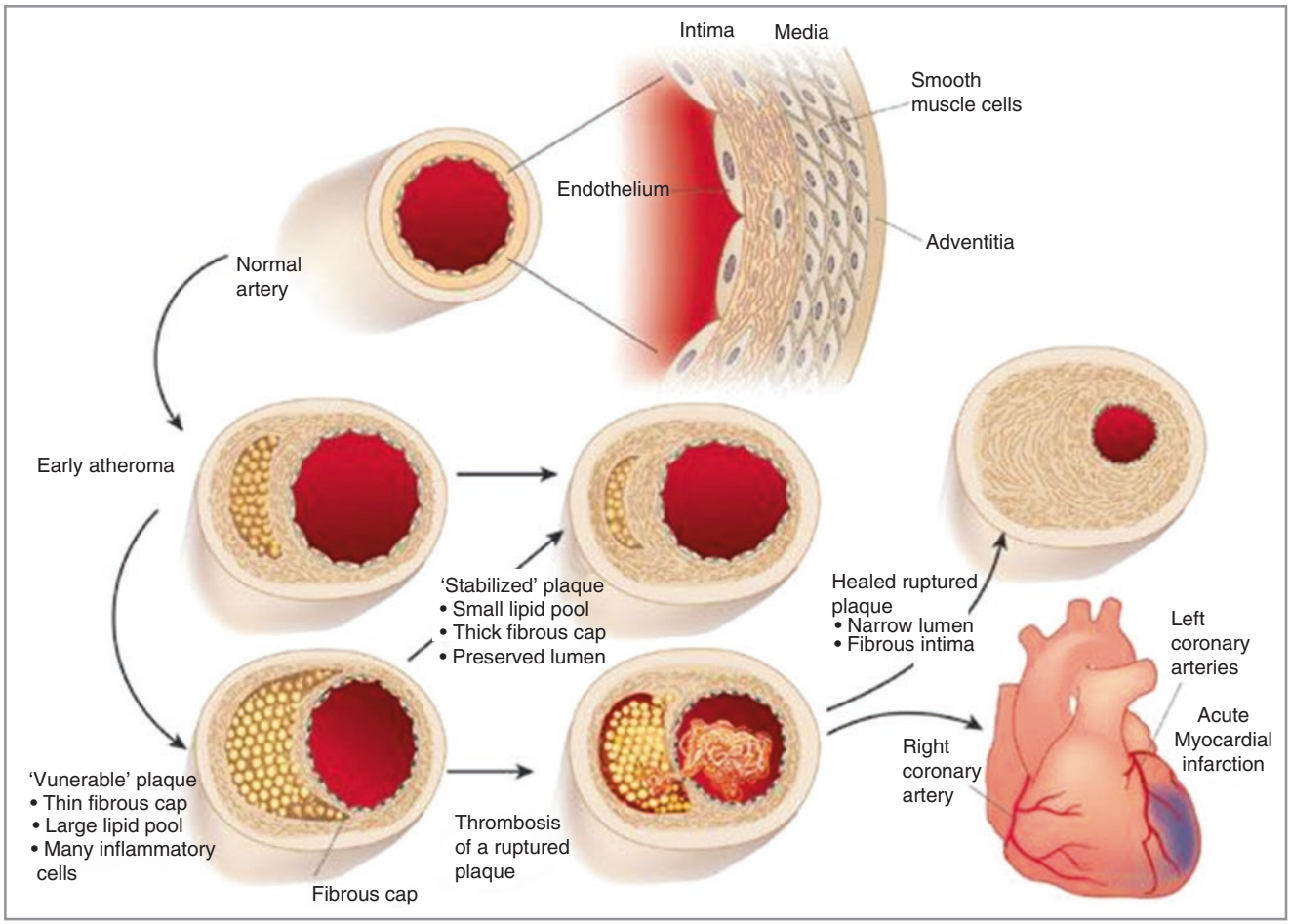

FIGURE 6-2

Progression of atherosclerosis and the role of inflammation in the stable vs. unstable plaque

NATURAL HISTORY

- For stable atherosclerotic plaques, severe stenoses (>70%) are typically associated with angina and ischemia, but clinical presentations may vary widely and multiple factors may influence the development of ischemia and angina.
- Angiographically intermediate stenoses (50–69%) may also result in angina and ischemia. However, assessing the functional significance of those lesions requires stress testing with imaging showing ischemia in the myocardial territory supplied by that coronary artery, or direct assessment of hemodynamic significance using adjuncts to coronary angiography:
  - Fractional flow reserve (FFR) or Instantaneous Wave-Free Ratio (iFR) measured during cardiac catheterization can assess the functional significance of lesions that are angiographically intermediate in severity.
  - Fractional flow reserve derived from CT angiography (CT-FFR) is an emerging noninvasive tool to evaluate the functional nature of a lesion, but its clinical use is currently limited [12].
- The ischemic cascade is characterized by a sequence of events, resulting in metabolic abnormalities, perfusion mismatch, regional and then global diastolic and systolic dysfunction, electrocardiographic (ECG) changes, and angina.

- When there is severe stenosis (>70%) or intermediate stenosis (50–69%) that is hemodynamically significant, ischemia occurs due to the inability of coronary blood flow to meet cardiac metabolic demand during exercise or stress.
  - For a similar degree of stenosis, the ischemic threshold is influenced by other factors including the degree of development of collateral circulation, coronary vascular tone, myocardial wall thickness, perfusion pressure, heart rate, afterload and co-morbidities such as anemia or pulmonary disease [13].
- Patients with nonobstructive or obstructive CAD are at risk of developing an ACS [14].
  - The hemodynamic severity of the atherosclerotic plaque prior to destabilization is frequently mild, but the plaques are lipid-rich and vulnerable to rupture or erosion [11, 15].

CLINICAL PRESENTATION, DIAGNOSIS, AND RISK STRATIFICATION

Signs and Symptoms

- The typical symptom in patients with chronic coronary artery disease is angina pectoris.
- William Heberden first introduced the term 'angina pectoris' in 1772 although its pathological etiology was not recognized until years later [16, 17].
  - Chest pain is characterized as typical angina, atypical angina, and non-cardiac chest pain (Fig. 6-3).
    - Angina is a syndrome that includes discomfort in the chest, jaw, shoulder, back, epigastric area or arm. The chest pain is aggravated by exertion or emotional stress and relieved by rest and/or nitroglycerin.
    - Atypical angina is generally defined by two of the above three features.
    - Non-cardiac chest pain is generally defined as chest pain that meets one or none of the above criteria.

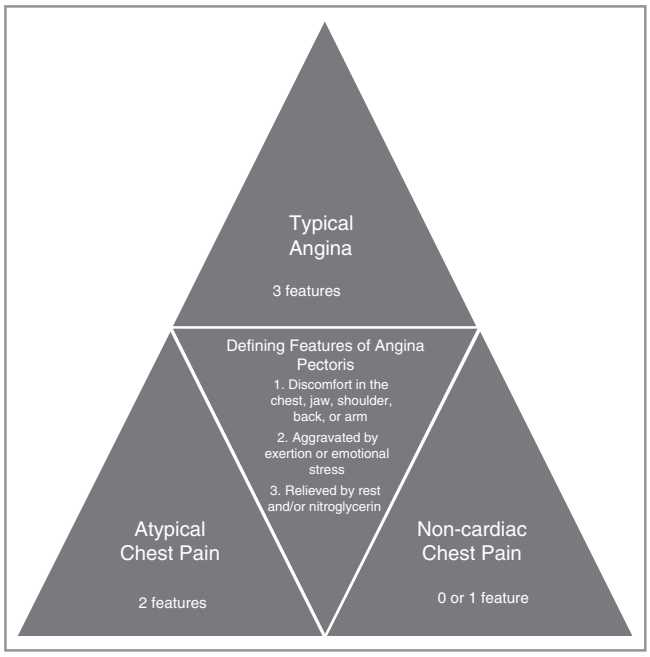

FIGURE 6-3

Definitions of typical angina, atypical and non-cardiac chest pain

TABLE 6-1

GRADING OF ANGINA PECTORIS BY THE CANADIAN CARDIOVASCULAR SOCIETY (CCS) CLASSIFICATION SYSTEM [18]

CLASS I	CLASS II	CLASS III	CLASS IV
Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals or in cold, or in wind, or under emotional stress. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition	Marked limitations of ordinary physical activity. Angina occurs on walking 1–2 blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace	Inability to carry on any physical activity without chest discomfort. Anginal symptoms may be present at rest

- Myocardial ischemia can present as typical angina pectoris, or as anginal equivalents. It may also be silent.
  - Anginal equivalents include dyspnea, palpitations, nausea, or epigastric discomfort. Dyspnea in these cases may also be due to ischemic left ventricular systolic or diastolic dysfunction, or ischemic mitral regurgitation.
  - In the absence of symptoms, silent ischemia requires demonstrating objective evidence of ischemia on stress testing.
  - Women, patients with diabetes, or those with prior MI or coronary artery bypass graft surgery are more likely to experience anginal equivalents or silent ischemia.
- The Canadian Cardiovascular Society (CCS) Classification (Table 6-1) is a useful tool to classify severity of angina based on the exertional threshold at which symptoms occur, determine the functional impairment of the patient and quantify response to therapy [18].
  - Alternative classification systems such as the Seattle Angina Questionnaire [19], which uses self-report in five domains (physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception) to assess the impact of angina on patients' health status, may also be used and may offer superior prognostic information.
- Physical signs in patients with angina pectoris are non-specific.
  - During or immediately after an episode of myocardial ischemia, a third or fourth heart sound may be heard.
  - A new murmur of mitral regurgitation may be apparent.
  - Other signs may include xanthelasma or xanthomas in patients with dyslipidemia, lung crackles, elevated jugular venous pressure and signs of left ventricular dysfunction in patients with heart failure, and other signs of vascular disease such as diminished peripheral pulses and vascular bruits.

Laboratory Testing

- In SIHD, laboratory tests are helpful in risk stratification and secondary prevention.
- Classical biochemical markers of myocardial injury such as troponin or CKMB are usually negative. However, high-sensitivity troponin (hs-Tn) may be elevated in those with stable coronary disease.

- Elevated hs-Tn is common in hospitalized patients and occurs as a result of myocardial injury. Elevated levels alone, however, are not sufficient to diagnose coronary artery disease.
- The fourth Universal Definition of MI defines the criteria for a type II MI, which is myocardial injury due to supply-demand mismatch. The Universal Definition criteria specify a rise and/or fall in hs-Tn, with at least one value above the 99th percentile of a normal healthy population, and evidence of myocardial oxygen supply-demand mismatch unrelated to coronary thrombosis and at least one of the following: symptoms, ECG changes or imaging evidence for loss of myocardial viability or function [20].
- Natriuretic peptides such as BNP or NT-proBNP may be elevated in those with SIHD and usually indicate worse prognosis [21].

■ Fasting plasma glucose or hemoglobin A1c (HbA1c) [22, 23] and lipid profile [24] should be evaluated in all patients with suspected or known coronary disease. Renal function should be evaluated in patients with chronic coronary disease.

- Renal dysfunction may occur due to associated vascular comorbidities and has a negative impact on prognosis in patients with CAD [25].

■ Additional laboratory testing, including cholesterol sub-fractions (ApoA and ApoB) [26], homocysteine [27], lipoprotein (a) [Lp(a)], coagulation profile, NT-proBNP [28], and markers of inflammation such as high-sensitivity C-reactive protein (hsCRP) [29, 30], may improve risk prediction in selected patients with SIHD, but their clinical utility remains unclear and approved targeted therapies are currently lacking.

■ Accumulating evidence from genetic, epidemiological, and translational studies support a causal role for Lp(a) in coronary artery disease, but there are several controversies regarding its role in clinical practice [31].

- In general, Lp(a) > 30 mg/dL is considered elevated and is associated with an increased risk of cardiovascular disease (CVD) [31].
- While emerging therapy with antisense oligonucleotides reduce Lp(a) levels in phase1 and 2 clinical trials [32, 33], there are currently no approved medications to lower Lp(a).

■ In the CANTOS trial, canakinumab, an inhibitor of interleukin-1β, reduced the risk of recurrent cardiovascular events in patients with recent ACS and hsCRP >2 mg/L [34, 35]. While the overall reduction in risk was modest and driven predominantly by decrease in recurrent MI, this was the first trial to show that specific anti-inflammatory therapy improved outcomes in patients with coronary artery disease. However, better understanding of risks such as infection and cost-effectiveness is needed prior to clinical adoption of this therapy. Subsequently, the COLCOT trial showed that in patients with recent myocardial infarction, colchicine at a dose of 0.5 mg daily compared to placebo lowered the risk of ischemic cardiovascular events [36].

Non-invasive Diagnostic Testing

■ **Resting electrocardiogram**

- All patients with suspected or known stable coronary artery disease should have a resting 12-lead ECG recorded.
  - ■ A normal or non-specific ECG is common and does not exclude the diagnosis of chronic myocardial ischemia.
  - ■ The resting ECG may show signs of CAD such as previous MI, ST depressions and/or T wave inversions.
  - ■ Other ECG findings may include left ventricular hypertrophy, bundle branch blocks, AV node block, atrial fibrillation, and frequent ventricular ectopy, all which can predict worse prognosis in patients with CAD.

■ Echocardiography

- Doppler echocardiography to assess for LV systolic and diastolic function, valvular abnormalities, and myocardial or pericardial disease is recommended in patients with known or suspected ischemic heart disease and a prior MI, pathological Q waves, signs and symptoms of heart failure, complex ventricular arrhythmias or an undiagnosed heart murmur (Class I) [37].

■ Stress Testing and Advanced Imaging

- Many patients with CAD will require stress testing or advanced imaging at some point to risk stratify and decide if invasive testing and treatment are indicated.
- The 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease recommends different stress modalities depending on whether the patient can exercise and has ECG abnormalities at baseline (Table 6-2) [37].
- The following sections summarize the indications for the use of stress testing with and without imaging in SIHD. For further details on stress testing modalities, please refer to Chap. 8.

TABLE 6-2

GUIDELINE EVIDENCE GRADING FOR DIFFERENT STRESS TESTING AND ADVANCED IMAGING MODALITIES IN PATIENTS WITH STABLE CAD [37]

MODALITY	ECG INTERPRETABLE?		ADDITIONAL CONSIDERATIONS	COR	LOE
	YES	NO			
Patient can exercise					
Exercise ECG	X			I	B
Exercise MPI or Echo		X	Not LBBB or pacing	I	B
Exercise MPI or Echo	X			IIa	B
Pharmacological stress CMR		X		IIa	B
CCTA		X		IIb	B
Pharmacological stress imaging (nuclear MPI, Echo, CMR) or CCTA	X			III	C
Patient unable to exercise					
Pharmacological stress with nuclear MPI or echo	Regardless			I	B
Pharmacological stress CMR				IIa	B
CCTA			Without prior stress test	IIa	C
Regardless of patient's ability to exercise					
Pharmacological stress with nuclear MPI or echo		X	LBBB present	I	B
Exercise/pharmacological stress with nuclear MPI, Echo, or CMR	Known coronary stenosis of unclear physiological significance being considered for revascularization			I	B
CCTA	Indeterminate result from functional testing			IIa	C
CCCTA	Unable to undergo stress imaging or as alternative to coronary catheterization when functional testing indicates moderate to high risk and angiographic coronary anatomy is unknown			IIb	C
Multiple imaging or stress studies at the same time	Regardless			III	C

■ Exercise ECG testing

- Exercise ECG is more sensitive and specific than the resting ECG for detecting myocardial ischemia.
- Horizontal or down-sloping ST segment depression of ≥1 mm defines a positive test with a sensitivity and specificity for the detection of significant coronary disease of 68% and 77%, respectively [38].
- However, test performance is lower in women compared to men. In women, the sensitivity and specificity are 61% and 70%, respectively. In men, the sensitivity and specificity are 72% and 77% [39].
- Exercise ECG testing is not of diagnostic value in the presence of left bundle branch block (LBBB), ventricular paced rhythm, ventricular pre-excitation (Wolff–Parkinson–White [WPW] syndrome), resting ST depression >1 mm, or baseline ST-T abnormalities in the presence of LV hypertrophy or digoxin use.
- ST elevations or new LBBB with angina, decreased exercise capacity (<5 METS), fall in systolic blood pressure or lack of increase in blood pressure during exercise, the appearance of a mitral regurgitation murmur, increasing ventricular ectopy or ventricular arrhythmias during exercise or in early recovery increase the probability of severe myocardial ischemia.
- The Duke treadmill score is a well-validated score that combines exercise time, ST-deviation, and angina during exercise to calculate the patient's annual mortality risk (Fig. 6-4) [40, 41].
- Interpretation of stress testing requires a Bayesian approach (Fig. 6-5).
  - The post-test probability of a true positive result is based on the pre-test probability of disease presence.
  - Diagnosis using the Bayes' formula is a probabilistic assessment (percentage likelihood) and not a binary decision (true or false).
- Diamond and Forrester described the relationship between clinical symptoms and angiographically significant CAD based on a Bayesian approach, predicting the likelihood of obstructive CAD based on age, sex, and type of chest pain symptoms (Table 6-3) [42].
  - Patients with symptoms of angina and intermediate pre-test probability of coronary disease based on age, gender, and symptoms, unless unable to exercise or have ECG changes that make ECG non-evaluable, are candidates for ECG stress testing as the initial assessment tool for diagnosis and risk stratification.
- Another common approach to evaluate the pre-test probability is to use an established risk score, such as the 2013 ACC/AHA Pooled Cohort ASCVD risk equation, further modified by the nature of symptoms at an individual patient level [43].

■ Imaging stress testing

- Stress imaging offers superior diagnostic performance, with generally higher sensitivity and at least comparable specificity, than exercise ECG testing for the detection of obstructive CAD.

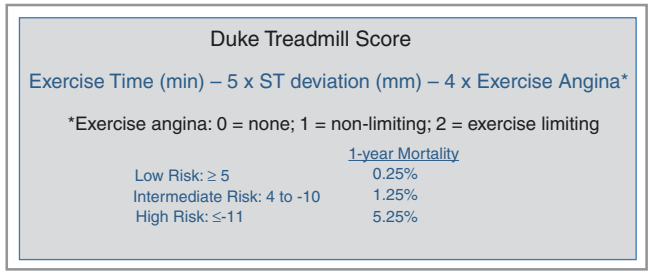

FIGURE 6-4

Duke Treadmill Score. Exclusions from the study included patients who are asymptomatic, have significant valvular or congenital heart disease, have uninterpretable ECG, had revascularization performed in the past or within 3 months after the exercise test, or with recent MI

FIGURE 6-5

Bayes' Theorem diagram. The post-test probability of disease after a test is influenced not only by the sensitivity and specificity of the test but also by the pre-test probability of disease. In patients with a low pre-test probability of disease (**A**), a positive test result will minimally increase the post-test probability and therefore have a low discrimination power. Similarly, in patients with high pre-test probability (**B**), a positive test will only confirm the presence of disease and therefore have a low discrimination power. The higher discrimination power of the test occurs in patients with intermediate pre-test probability of disease (**C**). For a given pre-test probability, the post-test probability becomes progressively higher as the test becomes more abnormal. As the sensitivity of the test increases, the negative test curve shifts further away from the line of identity. As the specificity of the test increases, the positive test curve shifts away from the line of identity

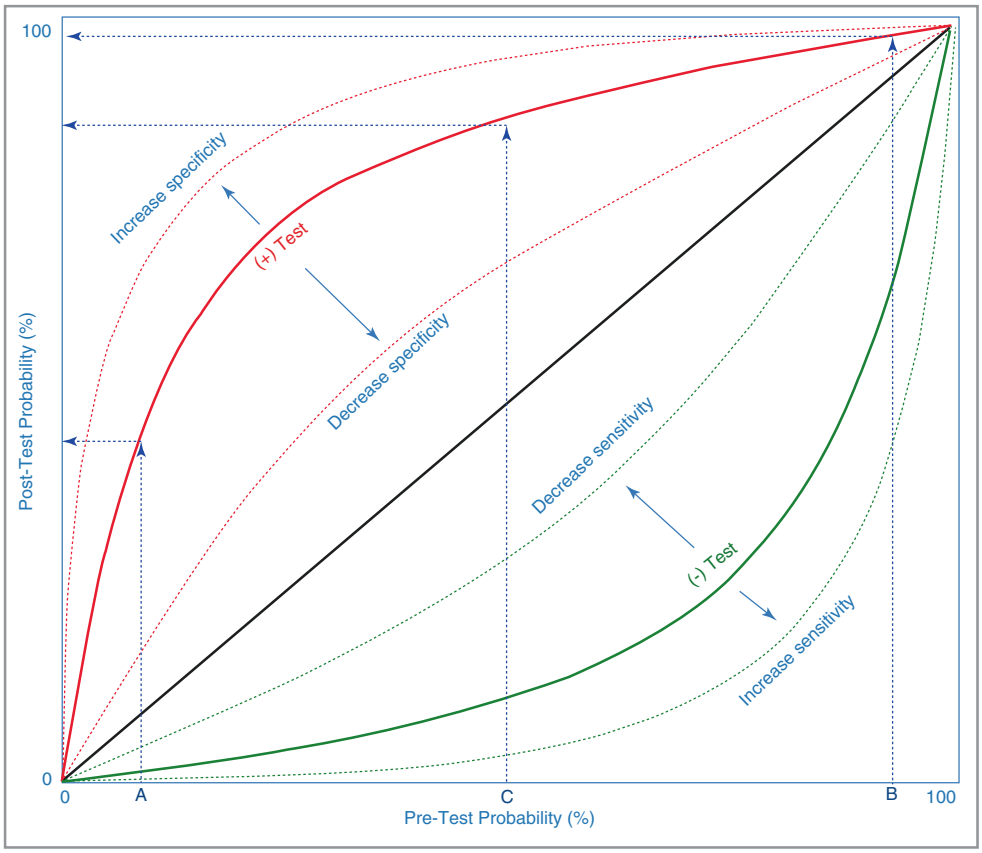

TABLE 6-3

PRE-TEST PROBABILITY OF CAD BY AGE, GENDER, AND SYMPTOMS

AGE (YEARS)	GENDER	TYPICAL ANGINA	ATYPICAL CHEST PAIN	NON-CARDIAC CHEST PAIN	ASYMPTOMATIC
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

High: Greater than 90% pretest probability. **Intermediate:** Between 10% and 90% pretest probability. **Low:** Between 5% and 10% pretest probability. **Very low:** Less than 5% pretest probability

- In patients with previous revascularization, stress imaging techniques are often preferred due to the ability to quantify and localize areas of ischemia.

– Myocardial perfusion scintigraphy using ^{201}Th and ^{99m}Tc radiopharmaceuticals are the most common imaging methods employing single photon emission computed tomography (SPECT) in association with an exercise test on either a stationary bicycle or a treadmill.
– The SPECT myocardial perfusion imaging Appropriateness Criteria recommends:

- For patients without symptoms:

  – Radionuclide stress imaging should be used only in high cardiovascular risk patients.

  - In asymptomatic patients with intermediate cardiovascular risk with a non-interpretable ECG, radionuclide imaging is of uncertain benefit.
- In symptomatic patients:
  - Radionuclide imaging is appropriate if (1) patients have an intermediate or high likelihood for CAD by pre-test assessment, or (2) patients have low likelihood of CAD but are unable to exercise or have a non-interpretable ECG.

- Pharmacological stress testing using vasodilator or dobutamine stress with either perfusion scintigraphy or echocardiography is indicated in patients who are unable to exercise adequately.
- High-risk features on stress imaging include transient ischemic dilation of the LV or severe ischemia in a large myocardial territory or multiple territories.
- Other potential imaging modalities that can be used to detect functional CAD are stress cardiac magnetic resonance imaging (MRI) and stress positron emission tomography (PET).

■ **Non-invasive techniques to assess coronary calcification and coronary anatomy**

- Cardiac computed tomography angiography (CCTA) using electron beam CT (EBCT) and multi-detector CT (MDCT) has been validated for the detection and quantification of the extent of coronary disease and calcification [44–46].
- The extent of coronary artery calcium (CAC) correlates with the overall burden of coronary atherosclerotic plaque. While CAC varies by race, gender, and age, it has been demonstrated to improve risk stratification in multiple cohorts including the Multi-Ethnic Study of Atherosclerosis (MESA) [47, 48].
  - The 2018 ACC/AHA guidelines state that evaluation of risk enhancers and CAC score may be considered if needed to assist with decision-making about statin therapy in patients aged 40–75 years old without diabetes with LDL-C ≥70 mg/dL–189 mg/dL who are at intermediate risk (10 year ASCVD risk ≥7.5% to <20% using the ASCVD Pooled Cohort Equation) (Class IIa) [49].
- The use of coronary CT angiography (CCTA) in stable angina is indicated in patients with a low pre-test probability of disease, with an inconclusive exercise ECG or stress imaging test.
  - The strength of CCTA is its strong *negative predictive value*. A negative scan excludes significant atherosclerosis.
- In the SCOT-HEART trial, the use of CCTA in patients with stable chest pain resulted in a significant reduction in death from CAD or nonfatal MI at 5 years compared to standard of care (2.3% vs. 3.9%; hazard ratio, 0.59; 95% confidence interval 0.41–0.84), without significantly higher rates of coronary angiography or revascularization [50]. Patients in the CCTA arm were more likely to start preventive therapy such as statins.

■ **Non-invasive Risk Stratification in Stable Ischemic Heart Disease**

- Risk stratification of patients with SIHD is important to determine the need for invasive testing and to identify those patients at highest risk, and therefore most likely to benefit from more aggressive treatment including revascularization (Table 6-4) [51].
- The clinical evaluation, response to stress testing, LV systolic function, and extent of CAD are elements which add incremental prognostic value.
- The incremental benefit of stress imaging test has been validated particularly in patients with stable angina and intermediate-risk Duke Treadmill Scores (AHA/ACC Class I indication for stress imaging).
- The negative predictive value of imaging stress testing is high. A normal stress perfusion study is associated with a subsequent rate of cardiac death and MI of less than 1% per year [52].

TABLE 6-4

NON-INVASIVE RISK STRATIFICATION OF CHRONIC STABLE CAD

HIGH-RISK (>3% ANNUAL MORTALITY RATE)	INTERMEDIATE RISK (1–3% ANNUAL MORTALITY RATE)	LOW-RISK (<1% ANNUAL MORTALITY RATE)
■ Severe resting left ventricular dysfunction (LVEF < 35%) ■ High-risk treadmill score (score < –11) ■ Severe exercise left ventricular dysfunction (exercise LVEF < 35%) ■ Stress-induced large perfusion defect (particularly if anterior) ■ Stress-induced multiple perfusion defects of moderate size ■ Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201) ■ Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201) ■ Echocardiographic wall motion abnormality (involving greater than two segments) developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min) ■ Stress echocardiographic evidence of extensive ischemia	■ Mild/moderate resting left ventricular dysfunction (LVEF 35–49%) ■ Intermediate-risk treadmill score (–11 < score < 5) ■ Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201) ■ Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving less than or equal to two segments	■ Low-risk treadmill score (score > 5) ■ Normal or small myocardial perfusion defect at rest or with stress[a] ■ Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress[a]

[a]Patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting left ventricular dysfunction (LVEF < 35%)

Invasive Diagnostic Testing

■ **Coronary angiography**

- Although coronary angiography cannot identify vulnerable atherosclerotic plaques that are likely to cause acute coronary events, the extent, severity, and location of CAD have been demonstrated to be important prognostic indicators in patients with stable angina.
- Invasive assessment of coronary anatomy in patients with SIHD is indicated when there is a high likelihood of severe obstructive CAD, particularly if symptoms are severe (CCS Class 3 or greater) and inadequately responding to optimal medical treatment (OMT).
- Other indications for coronary angiography include:
  - ■ Symptoms of angina with heart failure
  - ■ High-risk findings on stress testing
  - ■ Survivors of cardiac arrest
  - ■ Ventricular arrhythmias
  - ■ Recurrent angina in the setting of prior myocardial revascularization (either percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG])
  - ■ Inconclusive or conflicting data on non-invasive testing in patients who have an intermediate to high risk pre-test probability of CAD.

- **Adjuncts to Coronary Angiography**
  - Intra-coronary imaging modalities (intravascular ultrasound or optical coherence tomography) and coronary flow measurements (fractional flow reserve or instantaneous flow ratio) can help characterize the nature and severity of coronary stenosis.
  - **Intravascular Ultrasound (IVUS)** allows for accurate measurement of coronary luminal diameter, assessment of atherosclerotic lesions, and quantification of atheroma and calcium deposition. It is also an important tool to assess for interventional target lesions and stent placement.
  - **Optical Coherence Tomography (OCT)** provides high resolution imaging of the intraluminal and transmural structures of coronary arteries.
    - OCT can be useful to assess the mechanism of ACS and to optimize PCI. However, multiple barriers to its widespread use remain, such as cost, technical requirements, and operator skill [53].
  - **Fractional Flow Reserve (FFR)** is an invasive intracoronary assessment of functional severity of coronary lesions [54].
    - This technique involves inducing hyperemia through intracoronary injection of a vasodilator. FFR is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperemia. A normal value for FFR is 1.0 regardless of the status of the microcirculation, and an FFR < 0.80 indicates a functionally significant coronary stenosis [37, 51].
    - Three clinical trials (DEFER, FAME, and FAME2) support the use of FFR to guide revascularization in patients with stable angina, intermediate coronary stenosis and no prior ischemia testing [55–57]. In patient with FFR-negative lesions, OMT without PCI resulted in excellent outcomes. FFR-guided PCI for physiologically significant intermediate lesions resulted in reduced adverse events, driven by a reduction in urgent revascularization,
  - **Instantaneous Flow Ratio (iFR),** also known as instantaneous wave-free ratio, is an alternative to FFR that does not require vasodilator infusion. Multiple studies have validated that iFR is as at least as good as FFR to detect lesions causing ischemia [58].
    - iFR measures the physiological impact of a coronary stenosis on the distal coronary bed. An iFR value <0.89 is hemodynamically significant [59].
    - Two clinical trials (DEFINE-FLAIR and iFR-SWEDEHEART) support the use of iFR instead of FFR to evaluate intermediate coronary stenosis in patients with stable angina [55, 60]. Both studies showed that iFR is non-inferior to FFR in guiding revascularization of intermediate stenoses.

TREATMENT OF STABLE ISCHEMIC HEART DISEASE

- The goals of treatment of SIHD are to improve prognosis, reducing the risk of disease progression, MI and cardiac death, while improving quality of life and functional status by reducing symptoms.
- Secondary prevention measures should be implemented in all patients with SIHD.
- In patients with SIHD with angina, risk stratification and medical treatment of angina should be pursued, with an invasive treatment strategy reserved for patients at high-risk or with symptoms that are poorly controlled by medical treatment.

Secondary Prevention

- Co-existing cardiometabolic risk disorders should be corrected, with goals including blood pressure control to <130/80 mg/dL for hypertension [61], HbA1c to ≤7% for type-2 diabetes (T2D), and LDL-lowering to <70 mg/dL as will be discussed below.
- In the case of T2D, recent trials of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) liraglutide and semaglutide and of sodium-glucose co-transporter-2 inhibitors (SGLT-2i) empagliflozin, canagliflozin and dapagliflozin in patients with T2D and high cardiovascular risk or established CVD were associated with reduction in cardiovascular events [62, 63].
- Lifestyle changes should be pursued. These include weight management (BMI between 18.5 and 24.9 kg/m^2, waist circumference <102 cm in men and <88 cm in women), heart-healthy diet (reduced intake of saturated fats, trans fatty acids, and cholesterol), smoking cessation with the help of nicotine replacement therapy, and moderate-intensity aerobic exercise for 30–60 min at least 5 days and preferably 7 days a week [37].
- **Lipid-lowering therapy**
  - In patients with ASCVD, lowering LDL reduces the risk of cardiovascular death, MI, and stroke. The degree of risk reduction depends on baseline risk, and the potency of the LDL lowering therapy.
  - Statin (HMG-CoA reductase inhibitor) treatment reduces the risk of cardiovascular events in both primary and secondary prevention settings and is indicated in patients with CAD regardless of baseline cholesterol level.
    - Statins lower cholesterol effectively, but mechanisms beyond cholesterol synthesis inhibition, such as anti-inflammatory and antithrombotic effects [64, 65], may contribute to the cardiovascular benefit of statins.
    - High-intensity statin therapy lowers LDL levels by ≥50% in most people. Moderate-intensity statin therapy lowers LDL by 30% to <50%.
  - Multiple trials have shown a log-linear relationship between LDL reduction and reduction in incident cardiovascular disease (CVD) events, such that the degree in CVD risk reduction for any 1 mg/dL reduction in LDL is similar at any level of baseline LDL and with no evidence of threshold. In a meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration of 26 statin trials involving >170,000 patients, there was a 22% reduction in major vascular events per ~38 mg/dL (1 mmol/L) reduction in LDL. The degree of reduction in major vascular events was directly proportional to the absolute LDL reduction achieved [66].
  - Ezetimibe is a non-statin drug that reduces intestinal cholesterol absorption. It moderately lowers LDL levels (~15%) and is useful as an adjunct agent to statin therapy to achieve LDL goals or in patients who are intolerant to statins.
    - The IMPROVE-IT trial showed that in patients hospitalized for ACS in the past 10 days with LDL between 50 and 100 mg/dL on lipid lowering therapy or 50–125 mg/dL in those not on lipid lowering therapy, ezetimibe added to simvastatin 40 mg daily resulted in LDL lowering (53.7 vs. 69.5 mg/dL) and reduction in cardiovascular events by an absolute risk difference of 2% compared to simvastatin 40 mg daily alone [67].
  - PCSK-9 inhibitors (alirocumab, evolocumab) are injectable monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9. They lower LDL by up to 60% when added to statins.
    - The FOURIER trial showed that in patients with established CVD (prior MI, prior stroke or symptomatic PAD) and LDL ≥70 mg/dL, compared to statin therapy alone, evolocumab added to statin therapy decreased LDL levels to a median of 30 mg/dL (from 90 mg/dL) and reduced the absolute risk of cardiovascular events (composite of cardiovascular death, MI, stroke, unstable angina, coronary revascularization) by 1.5% over 2.2 years of median follow-up [68].

- The ODYSSEY Outcomes trial showed that in patients who had an ACS in the prior 1–12 months with LDL ≥ 70 on high-intensity statin therapy, alirocumab reduced the absolute risk of major adverse cardiovascular events (composite of CHD death, nonfatal MI, unstable angina, ischemic stroke) by 1.6% over 2.8 years of median follow-up. The ODYSSEY Outcomes trial showed a lower risk of death from any cause with the PCSK9 inhibitor, unlike the FOURIER trial, but neither trial showed a significantly lower risk of death from cardiovascular causes [69].
- Lowering LDL below current targets (e.g., median 30 mg/dL) with PCSK-9 inhibitors appears to be safe and effective [70].

– The 2018 ACC/AHA clinical practice guidelines for lipid management emphasize a more intensive approach in ASCVD patients with high intensity or maximally tolerated statin therapy to lower LDL by ≥50%, and using an LDL threshold of 70 mg/dL to consider the addition of non-statins to statin therapy especially in very high risk patients [49].

- "Very high risk" ASCVD patients include those having a history of two or more major ASCVD events (ACS in the past 12 months, history of MI or ischemic stroke, symptomatic peripheral arterial disease), or one major ASCVD event and two or more high-risk conditions (age ≥65, heterozygous familial hypercholesteremia, CHF, CABG, PCI, DM, hypertension, current smoking, CKD, persistently elevated LDL ≥ 100 mg/dL) [48].
- In patients with ASCVD who are ≤75 years old and not at very high risk, high-intensity statin therapy such as atorvastatin 80 mg daily or rosuvastatin 20 mg or 40 mg daily should be initiated with the aim of achieving ≥50% reduction in LDL levels (Class I). In patients >75 years old, moderate- or high-intensity statin could be used (Class IIa) depending on patient-specific factors such as the potential for risk reduction, drug-drug interactions, adverse effects, and patient preferences [49].
- In patients ≤75 years old with ASCVD who are not at very high risk, if LDL is >70 mg/dL despite maximally tolerated statin therapy, it may be reasonable to add ezetimibe (Class IIb) [49].
- In very high risk ASCVD patients, if LDL remains ≥70 mg/dL on maximally tolerated statin therapy, it is reasonable to add ezetimibe (Class IIa). Ezetimibe should be added to statin therapy before considering adding a PCSK9 inhibitor [49].
- In patients at very high risk whose LDL remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable (Class IIa), However, the long-term safety (>3 years) of PCSK9 inhibitors is uncertain and their cost effectiveness is low at current prices [49].

– The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines are similar to the 2018 ACC/AHA guidelines in emphasizing that lower LDL is better, using pharmacotherapy and healthy lifestyle habits to attain ≥50% lowering of LDL, with specific LDL thresholds to trigger consideration of non-statin therapy in "very high-risk" patients [71].

- However, the two guidelines differ in their definitions of "very high risk" patients. The ACC/AHA guidelines define this population as high-risk secondary prevention patients (as detailed earlier). In contrast, the ESC/EAS guidelines have expanded "very high-risk" to include those with documented ASCVD, either clinically (prior ACS, stable angina, revascularization, stroke, TIA, PAD) or unequivocally documented on imaging, as well as patients with DM (with target organ damage, or at least three major risk factors, or Type 1 DM >20 years), severe chronic kidney disease (CKD) (eGFR <30 mL/min/1.73 m^2), calculated SCORE of ≥10% for fatal CVD, or familial hypercholesterolemia (FH) with ASCVD or with another major risk factor.
- The ESC/EAS guidelines also differ from the ACC/AHA guidelines in their recommended LDL goals, favoring ≥50% LDL reduction and an absolute LDL goal <55 mg/dL in these "very high-risk" patients. For patients with ASCVD who have

a second vascular event within 2 years while on maximally tolerated statin-based therapy, an LDL goal <40 mg/dL may be considered. For those at "high" CV risk, ≥50% LDL reduction and LDL < 70 mg/dL is recommended.

- Triglycerides are not directly atherogenic but are associated with CVD risk and may be a secondary target of therapy. Clinical trial data about whether adding a second drug that targets triglycerides is beneficial in patients already treated with a statin who have high triglycerides levels are only recently emerging [72]. The REDUCE-IT trial showed that compared to placebo, the triglyceride-lowering agent icosapent ethyl (IPE) lowered the risk of ischemic events in patients with high triglycerides (135-499 mg/dL) who had CVD or were at high risk for developing CVD and had relatively well controlled LDLs on statin therapy, but IPE remains minimally used in practice at present [73].
  - Management of hypertriglyceridemia is primarily focused on intensive therapeutic lifestyle changes (weight loss, exercise, elimination of dietary trans fatty acids, reduction in intake of saturated fats and simple carbohydrates, increased intake of marine based omega-3 PUFA, and decreased alcohol intake), as well as strict glycemic control if patients are diabetic [72].
  - Pharmacologic therapy (fibrates or nicotinic acid) is indicated in those with very high triglycerides (>500 mg/dL) to prevent pancreatitis, or in those with a prior history of pancreatitis [72].
- While HDL levels are inversely associated with CVD risk, a growing body of evidence argues against a causal relationship. Raising HDL with niacin did not provide incremental benefit to statin therapy [74, 75]. Cholesteryl ester transfer protein (CETP) inhibitors markedly increase HDL levels but have so far failed to reduce the risk of cardiovascular disease [76]. HDL may therefore be a risk marker but not a target for intervention.

- **Antiplatelet agents**
  - Patients with ischemic heart disease should be treated with antiplatelet therapy unless there is a contraindication.
    - Aspirin 75–162 mg/day for life remains the cornerstone of pharmacological prevention of arterial thrombosis, reducing future risk of cardiovascular death, recurrent MI, and stroke in all patients with SIHD [77].
    - Clopidogrel may be an alternative agent in aspirin-intolerant patients, based on data from the CAPRIE trial [78].
  - Dual anti-platelet therapy (DAPT) refers to the combination of low dose aspirin (75–100 mg/day) and a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel).
  - DAPT is more effective than aspirin alone for SIHD but increases the risk of bleeding. Balancing this benefit/risk ratio depends on the clinical context.
  - Indications for DAPT fall into three categories: (1) after ACS, (2) after PCI with bare-metal stent (BMS) or drug-eluting stent (DES), or (3) in SIHD without ACS, BMS or DES.
  - DAPT After Acute Coronary Syndrome:
    - Following ACS, DAPT is recommended for at least 1 year [79].
  - DAPT After Percutaneous Stent Placement:
    - DAPT is indicated for at least 3 months following BMS placement and at least 1 year following DES placement.
    - Following stent placement, extending DAPT for 30 months could be considered, especially in higher risk patients. The DAPT score calculator [80] integrates patient and procedural characteristics to provide quantitative estimates of the cardiovascular benefits of extended DAPT vs. the risk of bleeding. It is meant as guidance for shared decision making rather than a recommendation for or against treatment.

- DAPT in SIHD Without Recent ACS or Stent:
  - While chronic DAPT is not routinely recommended in patients with SIHD, it could be beneficial in certain high-risk patients such as those with prior MI, stroke or peripheral artery disease (PAD), but at the expense of increased risk of bleeding [37, 77].
  - In those high-risk patients, the PEGASUS-TIMI 54 [81] and CHARISMA [82] trials showed improvement in cardiovascular outcomes at the expense of increased bleeding risk. Clinicians will need to strike a balance between efficacy and safety when considering DAPT for SIHD without recent ACS or stent.
  - In patients with SIHD who are on anticoagulation for other indications and are at increased risk of bleeding (HAS-BLED score ≥3) [83], it is reasonable to balance the risk of thrombosis vs. bleeding. American College of Chest Physicians Guidelines suggest that if patients are on warfarin, antiplatelet therapy could be avoided to minimize the risk of bleeding unless there are compelling conditions, such as recent coronary stent, coronary artery bypass graft, or mechanical valves (level IIC) [84].
- "Triple therapy" (DAPT and oral anticoagulation) refers to the use of DAPT in patients on anticoagulation (e.g., for atrial fibrillation) who undergo PCI. This is an active area of research due to the increased major bleeding risk.
  - The ISAR-TRIPLE trial compared 6-week to 6-month duration of clopidogrel after DES implantation in patients receiving concomitant aspirin and oral anticoagulation and found no different in the primary composite endpoint of death, MI, stent thrombosis, stroke, or major bleeding [85].
  - The REDUAL-PCI trial compared dual therapy (dabigatran and $P2Y_{12}$ inhibitor without aspirin) to triple therapy (warfarin, aspirin, and $P2Y_{12}$ inhibitor) in atrial fibrillation patients undergoing PCI. Dual therapy resulted in lower bleeding than triple therapy with no significant difference in the rate of thromboembolic events and death [86].
  - The WOEST trial randomized patients receiving oral anticoagulants and undergoing PCI to either clopidogrel alone ("double therapy") or clopidogrel plus aspirin (triple therapy) and found a reduction in bleeding and no increase in thrombotic events with double therapy [87].
  - The PIONEER AF-PCI trial of patients with atrial fibrillation undergoing PCI with stenting compared three groups: double therapy with a $P2Y_{12}$ inhibitor (clopidogrel in 95%) and low-dose rivaroxaban (15 mg daily), double therapy with very low dose rivaroxaban (2.5 mg BID), and triple therapy with warfarin. The double therapy groups had lower bleeding risk, but the trial was inconclusive for efficacy [88].
  - The AUGUSTUS trial found that in patients with atrial fibrillation who have had a recent acute coronary syndrome or have undergone PCI and are taking $P2Y_{12}$ inhibitor (mostly clopidogrel) for 6 months, a double therapy regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events compared to regimens that included a vitamin K antagonist, aspirin, or both [89].
  - With accumulating but still inconclusive data to guide management and extrapolating from the above trials, when considering triple therapy, it is best to assess the balance of ischemic, cardioembolic stroke and bleeding risks on an individual basis and using validated risk predictors (e.g. CHA2DS2-VASc, HAS-BLED scores), minimize the duration of triple therapy as much as possible with consideration of dual therapy only (oral anticoagulant and clopidogrel) in select patients, consider lower INR targets (2.0–2.5) if using warfarin, use clopidogrel as the $P2Y_{12}$ agent of choice, use low dose aspirin (≤100 mg), and consider adding a proton pump inhibitor in patients at high risk of gastrointestinal bleeding [77].
  - For more details on this subject, please refer to Chap. 4.

- **Beta-blockers**
  - Beta-blockers decrease myocardial oxygen consumption through reductions in heart rate, blood pressure, and myocardial contractility.
    - Beta blocker improve survival in patients with SIHD and history of prior MI or systolic heart failure [37].
    - Older post-MI studies have shown that beta-blockers can reduce the risk of cardiovascular death or recurrent MI by up to 30% [37, 90].
    - Metoprolol succinate, carvedilol, and bisoprolol have been shown to reduce mortality in patients with LVEF < 40% and heart failure or prior MI.
    - Beta-blockers should be used for 3 years in all patients with normal LV function after MI. They may be considered as chronic therapy for all patients with coronary or other vascular disease [37].
  - Beta blockers are first line therapy for relief of angina and ischemia. The dose should be titrated to achieve heart rate goal of 50–60 beats/min [37, 91, 92].
    - There have been no large trials assessing the effects of beta-blockers on survival or on rates of hard coronary events in patients with chronic stable angina in the absence of MI or systolic heart failure.
- **Angiotensin converting enzyme (ACE)-inhibitors**
  - ACE inhibitors, which reduce angiotensin II and increase bradykinin, are cardioprotective via multiple pathways, including lowering blood pressure and reducing LV hypertrophy, preventing remodeling and LV dilation following acute MI, and reducing atherosclerotic progression and plaque destabilization.
  - Multiple studies have demonstrated benefit in CVD outcomes, including reductions in ACS, death and need for revascularization, with using ACE-inhibitors in SIHD patients who are post-MI or who have co-existing hypertension, diabetes, systolic heart failure, LV dysfunction (EF ≤ 40%), or CKD unless contraindicated [93–95].
- **Angiotensin receptor blockers (ARBs)**
  - Treatment with ARBs and its impact on prognosis in ischemic heart disease has been less well studied than ACE inhibitors and results are mixed [96, 97].
  - ARB treatment may be appropriate in patients with SIHD when ACE-inhibition is indicated but not tolerated.
- **Aldosterone antagonists**
  - In patients with left ventricular dysfunction after an MI or in patients with SIHD and left ventricular ejection fraction ≤35%, the use of selective aldosterone-blocker therapy (eplerenone or spironolactone) in addition to standard therapy is recommended as it results in reduced morbidity and mortality [98, 99].

Anti-anginal Therapy in SIHD

- Medical therapy is the cornerstone of treatment for patients with SIHD, with an invasive treatment strategy reserved for patients at high-risk or with symptoms that are poorly controlled by medical treatment.
- Patients with stable angina should be treated with at least two classes of anti-anginal therapies to manage symptoms.
  - Triple anti-anginal therapy can be considered when optimal two drug regimens are insufficient to control symptoms.
    - Patients whose symptoms are poorly controlled on double therapy should be assessed for the need for revascularization.

■ **Beta-blockers**

- Most patients with SIHD are treated with beta-blockers even in the absence of angina, as detailed above.
- Beta-blockers are first line therapy for relief of angina. They dose should be uptitrated to achieve goal resting heart rates of 50–60 bpm [37, 91, 92]

■ **Calcium channel blockers (CCBs)**

- All CCBs dilate coronary and other arteries by inhibiting calcium influx via L-type channels, increase coronary blood flow, and decrease myocardial oxygen consumption. Choosing which CCBs to use in SIHD may be further influenced by differences between the two classes of CCBs:
  - Non-dihydropyridine CCBs (verapamil and diltiazem) reduce myocardial contractility, heart rate, and AV nodal conduction.
  - Dihydropyridine CCBs (e.g., nifedipine, amlodipine, and felodipine) are more potent vasodilators, do not affect cardiac conduction and have less cardiodepressant effects than non-dihydropyridine CCBs. Short acting dihydropyridines (nifedipine) should be avoided [100].
- If patients do not tolerate beta blockers or have persistent symptoms despite monotherapy, CCBs are recommended to treat angina. CCBs are especially effective in patients with vasospastic angina.
- CCBs reduce the risk of reinfarction in post-MI patients but in contrast to beta blockers, do not improve survival [101].
- Due to their cardiodepressant effects, dihydropyridine CCBs (verapamil, diltiazem) are associated with an increased risk of heart failure in patients with LV systolic dysfunction [102].

■ **Nitrates**

- The anti-ischemic effects of nitrates are primarily related to venodilation and reduced diastolic filling of the heart, which reduces myocardial oxygen demand and improves subendocardial perfusion. Coronary vasodilation and antagonism of coronary vasospasm may also contribute to the relief of symptoms.
- Rapidly acting formulations of nitroglycerin provide acute symptom relief in patients with angina.
- Long-acting nitrates reduce the frequency and severity of angina, prolong the duration of exercise before the onset of angina and ST-segment depression, and decrease the frequency of angina [103].
  - Nitrate tolerance may develop, resulting in poorer protection against angina and decreased efficacy of short-acting nitroglycerin.
  - Dosing should allow for a daily "nitrate free interval" to reduce the risk of tolerance.

■ **Ranolazine**

- Ranolazine is an anti-anginal drug whose mechanism of action is unclear; however, it alters sodium-dependent calcium channels, thus reducing the intracellular calcium overload that occurs during cardiac ischemia.
- Multiple trials of ranolazine in stable coronary disease patients showed improvement in angina, whether with monotherapy (MARISA) or as an add-on to other anti-anginal medications (CARISA and ERICA), or in patients with T2D (TERISA). The use of ranolazine for incomplete revascularization following PCI was not supported in the RIVER-PCI trial [104].
- Ranolazine does not alter heart rate or blood pressure which makes it useful when further up-titration of other anti-anginal medications is limited by hypotension or bradycardia.

- Ranolazine may prolong the QT interval on the ECG. It should therefore be reserved for use in patients who have failed other antianginal therapies.

■ **Other Anti-Anginal Therapies**

- Chelation therapy involves intravenous infusion of disodium ethylene diamine tetraacetic acid (EDTA) to improve blood flow and treat angina. Despite modest benefit in reducing angina in one clinical trial in SIHD patients, it is not recommended due to technical limitations of the trial and risks of disodium EDTA infusion which include hypocalcemia, renal failure, and death [105].
- Enhanced External Counterpulsation (EECP) involves using inflatable cuffs on the lower extremities that inflate in diastole and deflate in systole to increase diastolic blood flow. While studies are heterogeneous, there is an overall suggested benefit for EECP in patients with angina refractory to all other therapies [105].

Revascularization for SIHD

Revascularization in SIHD is indicated for patients who will have survival benefit from revascularization, or who have limiting symptoms despite optimal medical therapy (OMT).

■ **Coronary Artery Bypass Grafting (CABG)**

- Survival benefit with CABG may be seen with: [51]
  - Left main disease (≥50% stenosis) or left main equivalent disease
  - Three vessel CAD, especially with complex disease or LV dysfunction
  - Two vessel disease with >75% stenosis in the proximal LAD (i.e., proximal to the first major septal and diagonal)
    - CABG may also be favored in two vessel disease without proximal LAD disease if extensive ischemia is present.
- In patients with two- or three-vessel disease and DM, CABG (with LIMA) may be preferred over PCI.
  - The BARI-2D trial [106] enrolled patients with both diabetes and SIHD who were randomized in a 2 × 2 factorial design to undergo revascularization (with PCI or CABG as determined by the responsible physician caring for the patient) or OMT, and to undergo either insulin-sensitization or insulin-provision therapy to achieve HgBA1c < 7.0. At 5 years there was no overall significant difference in the primary endpoints of death and major cardiovascular events between study groups. However, revascularization significantly reduced major cardiovascular events in patients who underwent CABG, but not in those who underwent PCI, as compared with intensive medical therapy.
  - In the FREEDOM trial [107], 1900 patients with DM and multivessel disease were randomized to undergo either PCI or CABG. Patients who underwent CABG compared with PCI had a reduced risk of the composite outcome of all-cause mortality, nonfatal MI, or nonfatal stroke during 5 years of follow-up (18.7% with CABG vs. 26.6% with PCI, P = 0.005). The benefit of CABG was driven by decreased rates of MI (P < 0.001) and death (P = 0.049), whereas stroke was more frequent in the CABG group (5.2% vs. 2.4%, P = 0.03).
  - A survival benefit with CABG compared to PCI in patients with DM was also seen in subgroup analysis of the SYNTAX trial [108].
- The SYNTAX trial [109] compared CABG versus PCI (with first generation DES) in patients with left main or multivessel disease over a 12-month period and found higher rates of the combined endpoint of major adverse cardiac or cerebrovascular events at 12 months (17.8% vs. 12.4% for CABG, P = 0.002) largely due to increased rate of repeat revascularization in the PCI group (13.5% vs. 5.9%, P < 0.001). At 12 months, the rates of death and MI were similar between the two groups; stroke was significantly more likely to occur with CABG (2.2%, vs. 0.6% with PCI; P = 0.003).

- The SYNTAX score is an angiographic tool to grade the complexity of CAD. Patients with high Syntax score (>22) were more likely to benefit from CABG. Similar outcomes between PCI and CABG were observed in patients with lower SYNTAX scores [110]. As such, the score could be used as a quantitative measure of anatomic complexity to assist in the decision for PCI vs. CABG.

– The STITCH trial compared CABG and medical therapy to medical therapy alone in patients with heart failure and LVEF < 35%. While there was no significant difference in the primary endpoint of death from any cause with CABG vs. medical therapy alone, patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes [111].

■ **Percutaneous Coronary Intervention (PCI)**

– PCI may be considered in patients who would have survival benefit from revascularization but are unable to undergo CABG, or who do not have clear indications for CABG [51].
– Currently there are no data demonstrating clear survival benefit with PCI compared to OMT in patients with SIHD and no indication for CABG [112–116].
– PCI may be considered for:

- Single vessel disease (≥70% or 50–70% stenosis with FFR < 0.80 or iFR < 0.89)
  - If this involves the proximal LAD, or proximal left circumflex artery in a left-dominant system, and there are intermediate or high-risk findings on noninvasive testing, PCI is recommended over OMT alone.
- Two vessel CAD without involvement of the proximal LAD

– The COURAGE trial in 2007 showed that PCI as an initial strategy in stable CAD did not reduce the risk of death, MI or other major cardiovascular events when added to OMT over 4.6 years of median follow up [115]. The degree of angina relief was higher in the PCI group. Crossover to PCI for progressive symptoms or ACS was required in 32% of OMT patients. Most patients in the PCI arm received BMS since DES were not yet approved, although it remains unclear if there are significant differences in long-term rates of death or MI between DES and BMS.
– The COURAGE trial in 2007 and the BARI 2D trial in 2009 strongly argued against routine PCI for stable coronary disease, demonstrating comparable outcomes with PCI vs. OMT for death and MI.
– However, the FAME trial in 2009 and FAME 2 trial in 2012 showed benefit of FFR-guided PCI in selected patients with functionally significant coronary stenosis.

- In the FAME 2 trial [117], FFR-guided PCI with DES was more effective than OMT alone in reducing the primary composite end point of death, MI, or urgent revascularization over mean follow up of 213 days (4.3% in the PCI group and 12.7% in the OMT group, HR 0.32, 95% CI 0.19–0.53, P < 0.001). The difference was driven by a lower rate of urgent revascularization in the PCI group (1.6% vs. 11.1%; HR 0.13; 95% CI, 0.06–0.30; P < 0.001). Patients with stenoses that were not functionally significant had excellent outcomes with OMT alone. Due to premature termination of enrollment, the short follow up period may not have been sufficient to assess restenosis as a complication of PCI.

– The ORBITA trial in 2017 compared PCI to a sham procedure in patients with medically managed angina and severe single-vessel coronary stenosis (mean stenosis 84%, FFR 0.69, iFR 0.76) and found that PCI did not increase exercise time compared to the procedure [118]. These results suggest that symptomatic improvement from PCI may have a placebo component.
– The ISCHEMIA trial randomized patients with SIHD and moderate to severe ischemia on stress testing to an invasive approach (consisting of coronary angiography and then PCI or CABG as appropriate) or to medical therapy. Patients with ≥50%

left main stenosis, recent MI, prior PCI or CABG in the past year, unacceptable angina at baseline, LVEF < 35%, or NYHA Class 3–4 heart failure were excluded. There was no difference in the primary outcome of cardiovascular death, myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure at 3.3 years between the two groups. A companion quality of life study showed that in patients with daily, weekly or monthly angina (66% of the study cohort), there was significant improvement in symptoms with the invasive approach. These results further confirmed that invasive therapy in SIHD needs to be carefully considered, taking into account the burden of angina and the optimization of medical therapy [116].

- If either PCI or CABG are reasonable choices based on coronary anatomy and clinical factors, or if the choice between revascularization and OMT is unclear, shared decision-making considering patient preference (after discussion of the benefits and risks of the treatment options) and involvement of a multidisciplinary "Heart Team" may be beneficial.
- In patients with prior CABG, the presence of high-risk findings on noninvasive testing, greater severity of symptoms, or an increasing burden of disease in either the bypass grafts or native coronaries tends to increase the likelihood of an appropriate rating for revascularization.

SUMMARY AND CONCLUSIONS

- The diagnosis of SIHD is made based on symptoms, noninvasive stress testing demonstrating myocardial ischemia, and/or documentation of coronary atherosclerosis on imaging or angiography.
- Management of all patients with SIHD should include secondary prevention measures (including antiplatelet and statin therapy, aggressive control of cardiovascular risk factors, smoking cessation, weight control, regular exercise, and adoption of a heart healthy lifestyle) to reduce the risk of disease progression and improve prognosis, as well as therapies to relieve symptoms of angina.
- Revascularization is indicated if it will improve survival or relieve symptoms refractory to optimal medical treatment.

QUESTIONS AND ANSWERS

Question 1

A 59-year-old non-smoking man with hypertension, dyslipidemia, and family history of premature coronary artery disease presents to the cardiology outpatient clinic with a history of exertional chest pain that occurred a few times in the past month while he was playing basketball with friends. More recently, the chest pain occurred at lower levels of exertion while he was washing his car. The pain is in the left-side of his chest and radiates to his left arm, resolves after he stops exerting himself, and never occurs at rest. His baseline ECG is within normal limits. His current medical regimen includes a beta-blocker, diltiazem, hydrochlorothiazide (HCTZ), and a statin. A treadmill exercise stress test was obtained. He exercised in a standard Bruce protocol for 12 min and achieved 10 METS, reaching 88% of his maximal predicted heart rate with a normal blood pressure response to exercise. During the test he developed chest pain similar to his presenting symptoms at peak exercise that resolved at rest. His exercise EKG showed 2 mm horizontal ST segment depressions in leads II, III, aVF, V5, and V6 during peak exercise which resolved in the recovery phase. Myocardial perfusion images (SPECT) showed a moderate size reversible defect in the anterior and apical walls. The left ventricular systolic function was normal with an ejection fraction of 65% and there were no wall motion abnormalities, ischemic LV dilatation or increased lung uptake. He was then referred for invasive coronary angiography. The angiographic images are shown here (Fig. 6-6):

What is a true statement?

A. This patient should be treated medically with aspirin, statin, and beta-blocker, nitrates can be considered for symptomatic relief, but revascularization is not indicated at this time.
B. Revascularization is indicated and CABG is the method of choice.
C. This patient should be treated medically with aspirin, statin, and beta-blocker, and revascularization is indicated with PCI being the method of choice.

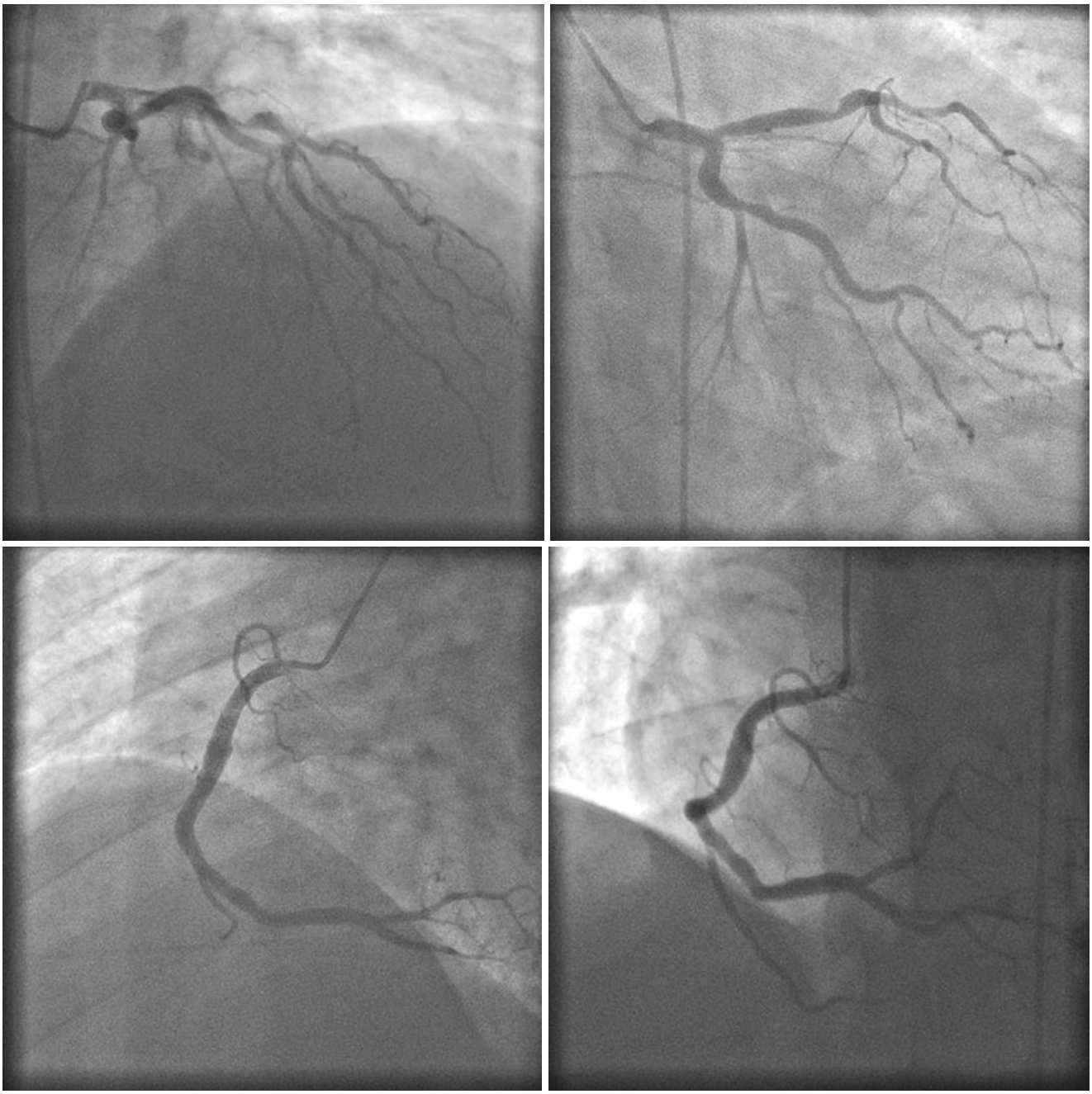

FIGURE 6-6

Angiographic images for Question 1

D. CABG is indicated in this case based on the location of coronary lesion.
E. Optimal medical treatment should be achieved prior to determine the need for revascularization.

1. Answer: C. This patient has an intermediate Framingham risk score (estimated 10-year risk of myocardial infarction or cardiovascular death 16%) and presented with typical chest pain features. His pre-test probability of coronary artery disease based on his risk factors and cardiac symptoms is intermediate to high. His Duke treadmill score was −6.0 with an estimated 1-year mortality of 1.3–2.9% placing him at moderate risk. Stress imaging showed intermediate risk findings (stress-induced moderate perfusion defect without LV dilatation or increase lung uptake with an intermediate risk Duke treadmill score) indicating the need for angiography. Coronary angiography showed a single obstructive mid LAD lesion. The patient is currently symptomatic (CCS class II) on beta-blocker, calcium-channel blocker, and statin therapy. Revascularization in this case is appropriate considering that the patient is already on medical treatment and is significantly symptomatic with intermediate-risk

perfusion defects on the stress test. Because he is not diabetic and has normal LV systolic function with single vessel disease not involving the left main coronary artery, the method of choice for revascularization is PCI.

Question 2

A 64-year-old man with diabetes, hypertension, and hyperlipidemia presents to his primary care physician's clinic complaining of exertional chest discomfort. He describes his chest discomfort as left-sided with radiation to his left arm, triggered by moderate exertion such as climbing stairs, and relieved by rest. His baseline EKG was within normal limits. His current medical regimen includes long acting insulin, an ACE-I, and statin. A treadmill exercise stress echocardiogram was obtained. The patient exercised in a modified Bruce protocol for 10 min and achieved nine METS with a hypotensive response to exercise at 82% of his maximal predicted heart rate. During the test he developed chest pressure at peak exercise that resolved after nitroglycerin was given. His exercise EKG showed 3 mm downsloping ST segment depressions in leads II, III, aVF, and aVL which persisted for 5 min into recovery. Stress echocardiographic images at peak exercise showed significant dilatation of the left ventricle and reduction of systolic function with anterior and anteroseptal wall hypokinesis. He was then referred for invasive coronary angiography. What is a true statement?

A. Isolated proximal right coronary artery disease will be present since leads II, III, and aVF had abnormal changes on his exercise EKG.
B. Dampening of pressure waveform during selective left coronary angiography is a potential finding.
C. Proximal left circumflex coronary artery disease is likely present because his baseline ECG is normal.
D. Multivessel coronary artery disease is unlikely to be present.
E. This patient will likely be a good candidate for percutaneous revascularization.

2. Answer: B. This patient has a very abnormal stress echocardiogram with findings suggestive of severe left main or multivessel coronary disease. Dampening of pressure waveform is present when there is significant stenosis of the left main and is a potential finding during this test. Isolated proximal right coronary artery is less likely to be the cause of his very abnormal stress test. Furthermore, ST changes during exercise, especially in the inferior and lateral leads, have low sensitivity in localizing ischemia and therefore are not used to define the location of coronary disease. However, greater ST segment depression involving multiple leads usually signifies extensive myocardial ischemia. A normal baseline EKG does not rule out significant coronary artery disease. Left circumflex artery disease is occasionally "silent" on EKG; however, his abnormal stress test is more likely to represent left main disease or multivessel coronary disease, and as such CABG will be the best choice of revascularization especially in the setting of diabetes.

Question 3

A 58-year-old woman with hyperlipidemia is admitted to the hospital with chest pressure at rest and an ECG showing ST depression in the anterior leads. Cardiac biomarkers were elevated and a diagnosis of a non-ST elevation myocardial infarction was made. The patient was started on aspirin, clopidogrel, low-molecular weight heparin, and beta blockers. Coronary angiography showed no obstructive coronary artery disease with only mild plaques in the left anterior descending artery. Left ventriculogram showed anterior wall hypokinesis and LVEF of 50%. What is a true statement?

A. A normal coronary angiogram rules out the presence of coronary artery disease.
B. Intravascular ultrasound will not show remodeling of the vessel wall, based on the Glagov hypothesis.
C. A sudden reduction in myocardial oxygen supply caused by non-obstructive atherosclerotic plaque rupture and thrombosis is probably the mechanism of ACS in this patient.
D. This patient has obstructive coronary artery disease.
E. This patient will benefit most from percutaneous coronary revascularization.

3. Answer: C. This patient has non-obstructive coronary artery disease and as such follows the Glagov hypothesis of progression of coronary artery disease and arterial remodeling. Intravascular ultrasound likely will show remodeling of the coronary vessel wall in this case. The NSTEMI was caused by a sudden reduction in myocardial oxygen supply caused by rupture or erosion of a non-obstructive atherosclerotic plaque and thrombosis. This patient will benefit most from optimal medical treatment alone rather than revascularization since there is no culprit obstructive coronary disease identified.

Question 4

A 55-year-old asymptomatic man with hypertension and hyperlipidemia, not on any medications, presents to the cardiology outpatient office due to an abnormal stress test obtained to evaluate exertional chest discomfort. His blood pressure in the office was 180/90 mmHg and his fasting lipid profile showed total cholesterol 210 mg/dL, LDL 150 mg/dL, HDL 34 mg/dL, and triglycerides 130 mg/dL. The exercise treadmill stress test showed 2 mm downsloping ST segment depressions in leads V5, V6, and aVL during peak exercise. He developed a hypertensive blood pressure response during exercise. He was then referred for coronary angiography that showed a 70% proximal lesion in a large obtuse marginal branch. The rest of the coronary arteries were angiographically normal. What is a true statement?

A. Percutaneous coronary revascularization is superior to medical treatment in this patient.
B. Medical treatment is superior to percutaneous coronary revascularization in this patient.
C. This patient will benefit from percutaneous coronary revascularization if his symptoms persist despite optimal medical treatment.
D. This patient should be started on medical treatment with aspirin, statin, and anti-hypertensive therapy before entertaining revascularization for his coronary artery disease.
E. Coronary revascularization can improve survival in this patient.

4. Answer D. This patient has exertional angina due to single vessel obstructive coronary artery disease. He would benefit from optimal medical treatment, including aspirin, statin therapy to lower LDL, and medications to control his blood pressure and heart rate before considering revascularization. If symptoms persist despite optimal medical treatment, revascularization in this setting can improve symptoms but will not affect survival outcomes. Based on the COURAGE trial results in patients with SIHD, there were no significant differences between the percutaneous coronary revascularization group and the medical therapy group in the primary event rate (composite outcome of death from any cause and non-fatal MI).

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CHAPTER 7

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Cardiovascular Disease in Women and in Pregnancy

CHAPTER OUTLINE

ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA	American Heart Association
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
AS	Aortic stenosis
AVR	Aortic valve replacement
BP	Blood pressure
BMI	Body-mass index
BMS	Bare metal stent
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAS	Coronary artery spasm
CRT	Cardiac Resynchronization Therapy
CO	Cardiac output
CV	Cardiovascular
CVD	Cardiovascular disease
DES	Drug eluting stent
DOAC	Direct oral anticoagulant
ESC	European Society of Cardiology
FMD	Fibromuscular dysplasia
HDL	High density lipoprotein
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HR	Heart rate
HTN	Hypertension
ICD	Implantable cardioverter defibrillators
IHD	Ischemic heart disease
LBBB	Left bundle branch block
LDL	Low density lipoprotein
LMWH	Low molecular weight heparin

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LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular event
MCS	Mechanical circulatory support
MFM	Maternal fetal medicine
MI	Myocardial infarction
MINOCA	Myocardial infarction with nonobstructive coronary arteries
MR	Mitral regurgitation
MS	Mitral stenosis
MV	Mitral valve
NSTEMI	Non-ST-elevation myocardial infarction
NYHA	New York Heart Association
OB	Obstetric
OCP	Oral contraceptive pill
PAMI	Pregnancy-associated myocardial infarction
PCI	Percutaneous coronary intervention
PMI	Point of maximal impulse
PPCM	Peripartum cardiomyopathy
PTT	Partial thromboplastin time
RV	Right ventricular
SAVR	Surgical aortic valve replacement
SCAD	Spontaneous coronary artery dissection
STEMI	ST-elevation myocardial infarction
STS	Society of Thoracic Surgeons
SVR	Systemic vascular resistance
TAVR	Transcatheter aortic valve replacement
TC	Total cholesterol
TG	Triglycerides
UFH	Unfractionated heparin
US	United States
VT	Ventricular tachycardia
VF	Ventricular fibrillation
VKA	Vitamin K antagonists

INTRODUCTION

- **Cardiovascular disease (CVD)** is the **leading cause of mortality** in women in the United States and globally.
  - In the 2016 AHA Update of the Heart Disease and Stroke Statistics report, nearly 400,000 (49.7%) women died from CVD [1].
  - CVD mortality exceeds mortality from all cancers combined.
  - In **young women** (age < 55 years), there has been an **increase in death** from CVD.
  - CVD is the leading cause of mortality among pregnant women
- Women's CV health is dictated by two features:
  - Sex differences from biological factors
  - Gender differences related to social, environmental, and community factors
- CVD in women is still underrecognized and undertreated.
  - **CVD risk factors** are **less aggressively** addressed in women.
  - Women are **less likely** to receive **guideline based care** for established CVD [2].

ISCHEMIC HEART DISEASE IN WOMEN

- **Risk Factors:** Applications of traditional Framingham risk factors including cholesterol, HTN, smoking, diabetes, and family history are different in men and women [3].
  - **Hypercholesterolemia**
    - *For men:* **total cholesterol** (TC) and **low density lipoprotein (LDL) cholesterol** are most predictive.
    - *For women:* The **TC/high density lipoprotein (HDL)** ratio is more accurate (target ratio ≥ 4).
    - *For* women > 65 years of age: **HDL and triglycerides (TG)** are more significant
    - ***Treatment:*** Women derive the same, if not greater, benefit from statin therapy for the primary and secondary prevention of CVD than men.
  - **Hypertension**
    - Hypertensive women have **3.5 times greater risk** of developing CVD than normotensive women.
    - Women are less likely to be diagnosed and treated for hypertension [4]
  - **Diabetes & Obesity**
    - One-third of US women are obese (body-mass index [BMI] ≥ 30 kg/m^2) and 7% are extremely obese (BMI ≥ 40 kg/m^2) [1].
    - Extremely obese women have a four times higher risk for CV events than lean women.
    - **Diabetes** related to obesity and metabolic syndrome is the **most powerful predictor of CV risk in women**—eliminates the CVD protection that premenopausal women enjoy.
  - **Cigarette Smoking**
    - **Tobacco use is the most important preventable cause of acute myocardial infarction (AMI)** in women (increases CVD risk sevenfold) [5].
    - MI in women is reduced within 1 or 2 years of smoking cessation and falls to the level of the risk of nonsmokers within 10–15 years.
  - **Depression**
    - **Depression is twice as prevalent** in women than men [6].
    - Depression increases a woman's risk for CVD by at least 50%.
    - Young women with AMI had 60% greater odds of having significant depression than young men [7].
- **Presentation:** The clinical presentation of ACS is different in men and women.
  - Most patients with AMI, both male and female, present with typical chest pain or discomfort, but women often present with atypical symptoms [8]:
    - Shoulder/neck pain
    - Abdominal pain
    - Profound fatigue
    - Dyspnea without fatigue
  - 2/3 of deaths from MI occur in women with no history of chest pain.
- **Pathophysiology:** Women are more likely to present with AMI without obstructive epicardial CAD.
  - **Plaque Rupture:** Disruption and infiltration of large necrotic core and thin fibrous cap
    - Most common cause of fatal MI in men (76%) and women (55%) [9]
    - Extremely uncommon among premenopausal women

- **MI with non-obstructive coronary arteries (MINOCA):** Is more common in younger patients and women [10].
  - **Coronary artery spasm:** Rare mechanism of MI in both men and women [11]
    - Smoking is a major risk factor
    - Women with coronary artery spasm were older, smoked less, and had less significant obstructive CAD compared with men with spasm.
    - Five-year MACE rates were similar in both sexes except **lower survival in younger women**
  - **Spontaneous coronary artery dissection (SCAD):** Rare cause of MI, more common in women [12]
    - Associated with **peripartum and postpartum status**, oral contraception pill use, connective tissue disease, and vasculitides including fibromuscular dysplasia (**FMD).**

- **Therapies—Revascularization:**
  - **Thrombolysis**
    - Early thrombolytic therapy is recommended in patients without contraindications who present to a hospital unable to perform percutaneous coronary intervention (PCI) and/or if there is an anticipated delay to performing PCI within 120 min of first medical contact (Class I, LOE A) [13].
      - Women treated with thrombolytics have higher morbidity and mortality: higher rates of shock, heart failure, reinfarction, recurrent ischemia, bleeding, and stroke compared with men.
      - **Female sex** is an **independent predictor of intracranial bleeding** with thrombolytic therapy [14].
      - Thrombolytic success (90-min patency rates and global ejection fraction) was similar between women and men.
  - **Primary PCI**
    - In pooled analysis of randomized trials of primary PCI versus thrombolytics in ST elevation MI patients, women had lower 30-day mortality with primary PCI.
    - An **early invasive strategy** is recommended in **women with non-ST segment elevation MI (NSTEMI) and high-risk features** (Class I, LOE) [15].
    - Women still have higher risk of in-hospital mortality following primary PCI as compared to men [16].
    - Women are at higher risk of non-central nervous system bleeding and vascular complications.
    - Newer generation drug eluting stents (DES) were associated with reduced death or MI and reduced target vessel revascularization compared with early-generation DES and bare metal stents (BMS).
  - **CABG**
    - No sex-specific studies of STEMI patients undergoing CABG [2].
    - Registry data show that women are older and sicker at time of CABG and had an increased risk of in-hospital mortality following CABG.
    - Women were less likely to receive an internal mammary graft and had more postoperative complications (renal failure, neurologic complications, and postoperative MI).

- **Therapies—Medical/Non-pharmacological**
  - The **2014 ACC/AHA NSTEMI guidelines** recommend that women with NSTEMI be treated with the **same pharmacological agents** as those used in men for both acute and secondary prevention of MI [17].

- Despite evidence for similar efficacy, women with AMI consistently receive less guideline-recommended therapies as compared to men.
- **Antiplatelet Therapies**
  - Weight and renal dosing of antiplatelet and anticoagulant agents should be considered in women because of higher bleeding risks (Class I, LOE B) [17].
  - **Aspirin** treatment in patients with AMI or prior vascular disease demonstrated similar efficacy in men and women [18].
  - **Clopidogrel** was associated with significant overall cardiovascular risk reduction compared to placebo in both men and women [19].
    - For women, risk reduction was only significant for MI (not for stroke or all-cause mortality).
    - For men, risk reduction for MI, stroke, and all-cause mortality were all significant.
  - No sex differences in efficacy and safety of the **potent P2Y12 inhibitors** including ticagrelor, prasugrel, and cangrelor [20].
  - Women have worse outcomes with **glycoprotein IIb/IIIa inhibitor (GpIIb/IIIa) treatment** than men in multiple trials [21].
    - No sex differences seen when further risk stratified by troponin level.
- **Anticoagulants**
  - Anticoagulant therapy is recommended for STEMI and NSTEMI patients regardless of revascularization strategy (Class I, LOE A) [13, 17].
  - Sex differences in anticoagulation therapy for AMI are not well described.
- **ß-blockers**
  - ß-blocker use in AMI is associated with similar reductions in mortality, sudden death, and reinfarction rate in both men and women [5].
  - Despite proven benefit, **ß-blockers are underutilized** in women.
  - Nonselective ß can exacerbate CAS and should be avoided in patients with spasm.
- **Statins**
  - Women experience **similar benefit** as men for secondary prevention [22].
    - Safety profile similar between both sexes.
    - Adverse events and discontinuation rates higher in women than men.
    - Statins are **contraindicated in pregnancy**.
- **Cardiac Rehabilitation**
  - **Cardiac rehabilitation after AMI** is a **Class I recommendation** for both men and women [13, 17].
    - Improves depression in women [23].
  - Referral, enrollment, and completion of cardiac rehabilitation is significantly lower in women than men.

ARRHYTHMIAS IN WOMEN

- **AF**
  - **Epidemiology**
    - AF is 1.5–2 times higher in men than women [24].
    - Despite higher incidence of AF in men, the lifetime risk of AF in women and men are similar because women live longer.

- **Risk Factors**
  - Advanced age, BMI, blood pressure, diabetes mellitus, valvular heart disease, HF, and MI.
- **Clinical Presentation**
  - Female sex is an **independent risk factor** for **AF-related stroke and systemic thromboembolism** [25].
  - CHA2DS2-VASc score is the recommended to predict risk stroke and guide anticoagulation with AF (1 point is given for female sex).
- **Treatment**
  - In adjusted analyses, there are no sex-specific differences in the utilization of rate versus rhythm control [26].
  - Women treated with rhythm control had higher incidence of adverse CV outcomes compared with women treated with rate control. No differences were seen in men [27].
  - No consistent data supporting sex-specific differences in antiarrhythmic therapy.
  - Major and minor complication rates following catheter ablation are higher in women than men.
  - Women are less likely to undergo catheter ablation for AF than men.
- **Stroke Prevention in AF**
  - **Warfarin**
    - Women treated with warfarin have a **higher residual risk of stroke or systemic embolism** than men [28].
    - No sex-specific differences in the risk of major bleeding among warfarin users have been demonstrated.
    - Female sex has been associated with lower time in therapeutic range.
  - **DOACs**
    - No sex-specific differences in the efficacy of stroke prevention between DOACs and warfarin have been demonstrated [29].
    - Unlike warfarin, women treated with a DOAC do not have higher rates of residual stroke or systemic embolism than men.
    - There are no significant sex-specific differences in the relative risk of major bleeding when comparing DOACs to warfarin.
    - Women treated with DOACs have lower rates of major bleeding than men.

HEART FAILURE IN WOMEN

- **Presentation and Causes**
  - Women with HF are older, more frequently hospitalized, and more likely to die than their male counterparts [30].
  - Men and women with HF present similarly, but women often present with higher burden of symptoms.
  - Ischemic heart disease accounts for fewer cases of HF in women than men.
  - Stress cardiomyopathy develops more commonly in women.
- **HF with reduced ejection fraction, HFrEF** [31]
  - Women are 65% less likely to develop HFrEF than men.
  - Diabetes and obesity significantly increase the risk of HFrEF in women as compared to men.

- Women with HFrEF have a higher prevalence of **nonischemic cardiomyopathy** when compared to men.
- Women have a better overall survival with HFrEF than men, but women with IHD have worse mortality than their male counterparts.

■ **HF with preserved ejection fraction, HFpEF**

- HFpEF is more common in women than men.
- Female myocardium is more likely to remodel in a concentric pattern in contrast to men who undergo eccentric hypertrophy.
- Risk factors for HFpEF include HTN, obesity, and AF.

■ **Medical Therapies for HF:** similar benefits among men and women with ACEi, ARBs, aldosterone antagonists, and β-Blockers [32]

■ **Implantable cardioverter-defibrillator, ICD**

- Women are underrepresented in all trials of ICDs.
- ICD therapy demonstrated a similar benefit in men and women for:
  - Secondary prevention following VT/VF [33]
  - Post MI LV dysfunction

■ **Cardiac resynchronization therapy, CRT**

- Women with HFrEF derive **superior benefit from CRT** than their male counterparts.
  - Women had an 18% lower mortality risk after CRT [34].
  - Women with LBBB had a 21% lower mortality risk than men.
- Women benefit from CRT at shorter QRS intervals than men.
  - Women with QRS duration 120–129 ms had a higher mortality benefit than men.
- Current guidelines for CRT are not gender specific.
- Women are less likely to receive an indicated CRT.

■ **Mechanical circulatory support, MCS/Cardiac Transplantation**

- **MCS**
  - MCS referral and implantation is less common in women than men.
  - At time of implantation, women are more frequently in cardiogenic shock than men.
  - Women with continuous-flow left ventricular assist device (LVAD) as a bridge to transplant had similar rates of survival as men but were less likely to undergo heart transplantation [35].
  - Post-implantation complications including longer ventilatory and inotrope support, neurologic complications, and perioperative right ventricular failure are more common in women than men.
- **Cardiac Transplantation**
  - The number of women receiving cardiac transplants is increasing (19.3% from 1992 to 2000 to 23.7% from 2006 to 2011) [36].
  - Women with listed for transplantation have higher mortality than men, are less likely to be bridged to transplant with an LVAD or total artificial heart, more likely to be removed from the waiting list.
  - **Post-transplant mortality** is **similar** in men and women.
  - Women are less frequently referred to cardiac transplant.
    - Lower prevalence of ischemic heart disease
    - Higher levels of panel reactive antibodies due to previous pregnancies or miscarriages
    - More self-refusal

VALVULAR HEART DISEASE IN WOMEN

- **Aortic stenosis, AS**
  - **Presentation**
    - *Clinical characteristics:* older, more New York Heart Association III/IV symptoms, porcelain aorta, moderate or severe mitral regurgitation (MR), and renal failure [37]
    - *Imaging characteristics:* more concentric hypertrophy, smaller LV size and volume, greater LVEF, and less myocardial fibrosis
    - Paradoxical low flow-low gradient AS more common.
    - Women in the Society of Thoracic Surgeons (STS)/ACC Transcatheter Valve Therapy Registry (TVT) had higher STS scores and were considered frailer by Heart Valve teams.
    - Referrals to aortic valve replacement (AVR) were lower in women than men.
  - **Outcomes after surgical AVR**
    - Female sex is an independent risk factor for mortality after surgical AVR
    - Patient prosthesis mismatch after surgical AVR is more common in women.
  - **Outcomes after trans-catheter AVR (TAVR)**
    - Females undergoing **TAVR** have **better long-term survival** [38].
      - Women who underwent transfemoral TAVR had lower 30-day and 1-year mortality compared to women who underwent SAVR [39].
      - Despite immediate post-procedure complications, short-, mid-, and long-term outcomes are more favorable in women compared to men.
    - Procedural complications including annular or ventricular rupture, coronary obstruction, vascular complications, and post-procedural bleeding are more common in women.
- **MR**
  - **Presentation**
    - Women tend to have anterior or bileaflet prolapse whereas men more commonly have posterior leaflet prolapse [37].
    - Women have more calcification of the mitral annulus.
  - **Outcomes after Surgical Management**
    - Women had greater mitral gradients and higher incidence of recurrent HF post-surgery.
    - Women underwent surgical replacement more often than men.
    - Among men and women presenting for mitral repair, more women needed conversion to valve replacement.
    - Women had worse long-term survival after mitral repair. No sex differences exist in survival after replacement.
  - **Outcomes after MitraClip**
    - Similar overall short-term outcomes for MitraClip in men and women [40].
    - High rates of procedural success in both men and women.
    - Post procedure, there was a significant reduction in LV volume and improvement in LVEF in both sexes, but there was a trend toward more improvement in NHYA class in men.

CARDIOVASCULAR DISEASE IN PREGNANCY

- **Normal hemodynamics of pregnancy** [41, 42]: Significant hemodynamic shifts occur with normal pregnancy (Fig. 7-1) including:
- Increase in heart rate and plasma volume resulting in an increase in cardiac output of 30–50%
- Fall in systemic vascular resistance due to maturation of the low-resistance placental circulation and hormonal effects
- Fall in systolic and diastolic blood pressure (5–10 mmHg) due to local vasodilatory effects, with blood pressure nadiring in the second trimester and gradually rising thereafter
- Physiologic anemia, resulting from a greater increase in plasma volume as compared to red blood cell mass
- Decrease in pulmonary vascular resistance (~24%) by 8 weeks of gestation. Thus, mean pulmonary artery pressure should not increase in normal pregnancy.

With delivery:

- Cardiac output increases further (50% during active labor and up to 80% immediately post-partum as compared to pre-labor values) mainly due to pain-mediated catecholamines
  - Dense epidural anesthesia can significantly reduce swings in heart rate and BP and is often utilized during delivery of patients with CV pathology
- Preload increases due to 300–500 mL autotransfusion from the uterus and lower extremities after relief of inferior vena cava pressure with delivery
- 500 mL (for vaginal delivery) and 1000 mL (for caesarian section) of blood loss is expected
- Systemic vascular resistance increases after placental delivery
- Hemodynamics largely return to baseline values by 2 weeks postpartum but do not completely normalize until 6 months or longer

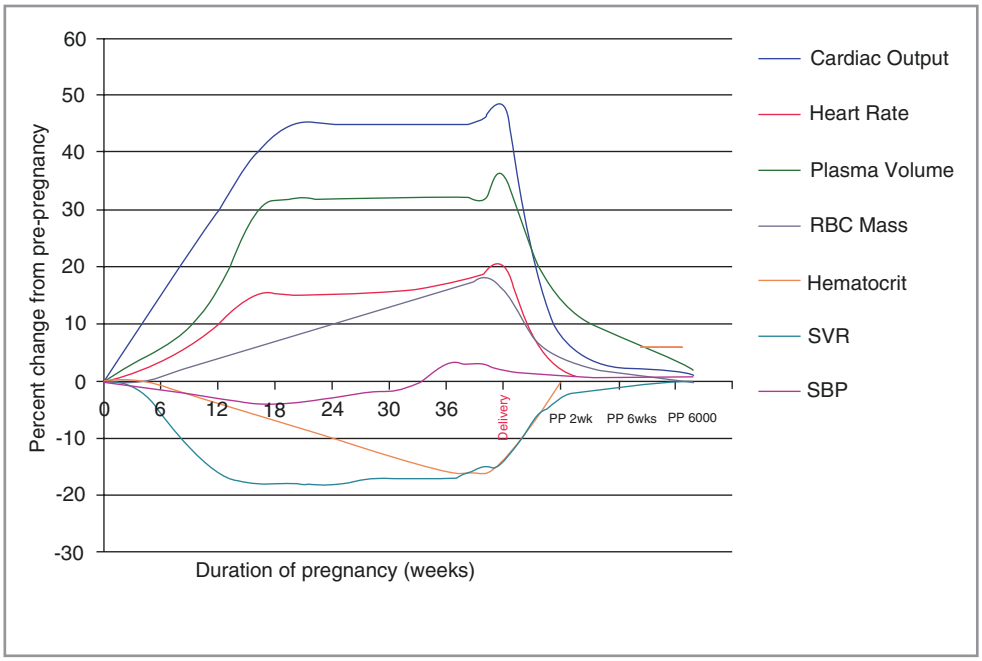

FIGURE 7-1

Normal hemodynamics of pregnancy (Permission already obtained from Yucel E, DeFaria Yeh D. Pregnancy in Women with Congenital Heart Disease. Curr Treat Options CardioMed (2017) 19:73). *PP* postpartum, *RBC* red blood cell, *SBP* systolic blood pressure, *SVR* systemic vascular resistance

Physical exam findings with normal pregnancy [41]:

- Increase in respiratory rate and heart rate
- Jugular venous pulsations are more prominent but should not be elevated
- Diffuse, displaced PMI
- Palpable RV impulse
- Louder S1 with persistent splitting of S2
- S3 can be normal in pregnancy
- Flow murmurs: systolic ejection murmur over the left lower sternal border

Echocardiographic features of normal pregnancy:

- Due to wide-spread availability and safety of use during pregnancy, echocardiography should be utilized in cases of suspected CV pathology
- During normal pregnancy [43]:
  - There may be an increase in the size of all cardiac chambers as compared to non-pregnant values, but dilation should not exceed the upper limits of normal
  - Chamber dilation may result in annular dilation and in turn an increased incidence of physiologic regurgitation of the mitral, tricuspid, and pulmonary valves. Aortic regurgitation, however, should not occur in normal pregnancy.
  - Biventricular function should remain within normal limits
  - A pericardial effusion is a common (40%) finding in normal pregnancy [44]

Pre-conception counseling:

- Patients with pre-existing CVD should be managed during pregnancy by a multidisciplinary team during pregnancy including specialists from Maternal-Fetal Medicine, Cardiology, Obstetric Anesthesia, and Interventional Cardiology and/or Cardiac Surgery (when an intervention may be required). When possible, evaluation and a complete discussion of potential risks should take place prior to conception.
- Pre-conception, cardiologists should discuss [45]:
  - Maternal cardiac risk
  - Fetal risk
  - Genetic consultation when appropriate
  - Modification of CV medications prior to conception, including discontinuation of teratogenic medications
  - Plan for post-pregnancy contraception
  - Pre-conception testing to aid in risk assessment
    - Consider exercise testing for evaluation of functional capacity, especially in women with asymptomatic severe valvular stenosis
    - Consider cardiopulmonary exercise testing in women with complex congenital heart disease
    - Consider obtaining a preconception transthoracic echocardiogram both to aid in risk assessment and to use as a referent during pregnancy
    - Consider obtaining an amino-terminal pro-B type natriuretic peptide prior to conception to aid in risk assessment and use as a referent during pregnancy
    - Ensure imaging of the entire aorta in those with aortopathies
- Several risk scores have been developed to assist in preconception counseling and risk-assessment of women with pre-existing congenital heart disease during pregnancy including CARPREG (and more recently CARPREG II) [46], ZAHARA [47], and mWHO [42] (Table 7-1).
- All women with congenital disease should undergo fetal ultrasound for fetal cardiac screening.
- The most common CV events among pregnant women with pre-existing CVD include arrhythmia, heart failure, and thromboembolic events [45].

TABLE 7-1

AVAILABLE CARDIAC RISK SCORES FOR PRE-CONCEPTION COUNSELING AND MATERNAL RISK STRATIFICATION

CARPREG II	ZAHARA	MWHO
■ Prior cardiac events or arrhythmias (3 pts) ■ NYHA III-IV functional class or cyanosis (3 pts) ■ Mechanical valve prosthesis (3 pts) ■ Ventricular dysfunction (2 pts) ■ High risk left-sided valve disease/LVOT obstruction (2 pts) ■ Pulmonary hypertension (2 pts) ■ Coronary artery disease (2 pts) ■ High risk aortopathy (2 pts) ■ No prior cardiac intervention (1 pt) ■ First antenatal visit >20 weeks gestation (1 pt) **Score: Maternal Risk** 0–1: 5% 2: 10% 3: 15% 4: 22% >4: 41%	■ Prior arrhythmia (1.5 pt) ■ NYHA III-IV functional class (0.75 pt) ■ Left heart obstruction (LVOT gradient >50 mmHg, AVA < 1 cm^2, 2.5 pts) ■ Mechanical valve prosthesis (4.25 pts) ■ Moderate-severe subpulmonic or systemic atrioventricular valvular regurgitation (0.75 pts) ■ Pre-pregnancy cardiovascular medications (1.5 pts) ■ Cyanotic heart disease (either repaired or unrepaired, 1 pt) **Score: Maternal risk** <0.5: 2.9% 0.51–1.5: 7.5% 1.51–2.5: 17.5% 2.51–3.5: 43.1% >3.5: 70%	Class I: Low risk (MCER 2.5–5%) ■ Mild/uncomplicated: PS, PDA, MVP ■ Repaired PDA, ASD, VSD, anomalous pulmonary venous drainage ■ Isolated atrial/ventricular ectopic beats Class II: Mild risk (MCER 5.7–10.5%) ■ Mild/uncomplicated uncorrected ASD/VSD ■ Repaired TOF ■ Most arrhythmias ■ Turner's syndrome without aortic dilation Class II–III: Intermediate risk (MCER 10–19%) ■ Mild LV dysfunction (LVEF > 45%) ■ HCM ■ Valvular heart disease not considered class I or IV ■ Marfan's and inherited thoracic aortic syndromes without aortic dilation ■ Bicuspid with aortic dimension <45 mm ■ Repaired coarctation ■ Atrioventricular septal defect Class III: Significant risk (MCER 19–27%) ■ LVEF 30–45% ■ Previous PPCM with preserved LVEF ■ Moderate MS ■ Severe asymptomatic AS ■ Mechanical valve prosthesis ■ Systemic RV with preserved function ■ Fontan circulation in a clinically stable patient ■ Unrepaired TOF ■ Other complex congenital heart disease ■ Marfan's or other inherited thoracic aortic syndrome with 40–45 mm aortic dilation ■ Bicuspid with 45–50 mm aortic dilation ■ Turner's syndrome with an index aortic size 20–25 mm/m^2 ■ TOF with ascending aortic dilation <50 mm ■ VT ■ Unrepaired cyanotic heart disease Class IV: Very high risk, pregnancy not recommended (MCER 40–100%) ■ Severe MS ■ Severe symptomatic AS ■ PAH ■ LVEF < 30% or NYHA III-IV functional class ■ Prior PPCM with residual LV dysfunction ■ Systemic RV with moderate-severe dysfunction ■ Uncorrected severe coarctation ■ Marfan or other inherited aortic syndrome with >45 mm aortic dilation ■ Bicuspid with >50 mm aortic dilation ■ Turner's syndrome with an indexed aortic size >25 mm/m^2 ■ TOF with ascending aortic dilation > 50 mm ■ Vascular EDS ■ Severe coarctation ■ Fontan with any complication

AS aortic stenosis, *ASD* atrial septal defect, *AVA* aortic valve area, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *MCER* maternal cardiac event rate, *MS* mitral stenosis, *MVP* mitral valve prolapse, *NYHA* New York Heart Association, *PDA* patent ductus arteriosus, *PPCM* peripartum cardiomyopathy, *PS* pulmonary stenosis, *TOF* tetralogy of fallot, *VSD* ventricular septal defect

Contraception [41, 42]:

- Contraception should be discussed with all women of reproductive age, particularly those with cardiovascular conditions or on potentially teratogenic medications for whom pregnancy (if desired) should be carefully planned
- At every CV visit, women of reproductive age should be asked about their desire for pregnancy in the upcoming year to enable discussions surrounding preconception counseling
- Oral contraceptives containing estrogen should be avoided in patients with a history of hypertension, thrombosis, ischemia, or cyanosis
- Progesterone-only oral contraceptives, intrauterine devices, and sterilization (when future pregnancy is not desired) remain options for women with pre-existing CVD desiring contraception.

Pre-eclampsia [42]:

- Is a leading cause of maternal and fetal morbidity and mortality
- Defined as development of new hypertension (systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg on two occasions at least 4 h apart) with onset ≥20 weeks of gestation, and proteinuria or (in the absence of proteinuria) new onset thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral/visual symptoms
- Low-dose aspirin is recommended after the 12th week of gestation for pre-eclampsia prevention among women at elevated risk for pre-eclampsia: those with a history of pre-eclampsia, chronic hypertension, diabetes, renal disease, autoimmune diseases, and multiple gestations
- Women with a history of gestational hypertension (including pre-eclampsia) and gestational diabetes are at elevated risk for future CVD
  - As such, the **AHA now recommends obtaining a pregnancy history** as part of routine CVD risk assessments in women [3]

VALVULAR HEART DISEASE: SEE TABLE 7-2 [41, 42]

Prosthetic valves:

- Prosthetic valves (especially mechanical) pose an increase the risk of adverse maternal events during pregnancy [46, 48]
- Valve repairs should be performed when possible in women of child-bearing age to avoid the need for valve prostheses
- When valve repair is not possible, consider bioprosthetic valves in women who may desire pregnancy [42]:
  - Lower risk of thrombosis and do not require systemic anticoagulation
  - However, higher rate of deterioration than mechanical prostheses
    - Whether pregnancy accelerates structural valve deterioration remains controversial.
- Mechanical valves:
  - Confer an increased risk of mortality during pregnancy as well as major complications, including valve thrombosis and maternal and fetal hemorrhage [48–50]
  - Anticoagulation: required for mechanical valves during pregnancy
    - Optimal means of maintaining therapeutic anticoagulation during pregnancy remains controversial
    - Anticoagulation poses a significant challenge due to the risks of teratogenic effects with warfarin, fetal hemorrhage with agents that cross the placenta, and maternal hemorrhage at time of delivery.
    - Use of epidural anesthesia (as is often recommended for deliveries in women with pre-existing CVD) is contraindicated in the anticoagulated patient. **The American Society of Regional Anaesthesia** recommend holding unfractionated heparin

TABLE 7-2

MANAGEMENT OF VALVULAR HEART DISEASE IN PREGNANCY

MANAGEMENT OF VALVULAR HEART DISEASE IN PREGNANCY

Mitral Stenosis:
- Etiology: most commonly rheumatic disease
- Intervene preconception if valve area less than 1.0 cm^2 and consider in patients with a valve area <1.5 cm^2
- Symptomatic pregnant patients should be treated with β1 selective blockers for heart rate reduction and activity restriction. If symptoms persist despite adequate heart rate control, add diuretic therapy.
- Percutaneous mitral valvuloplasty should be considered for persistent symptoms and/or pulmonary hypertension (PASP > 50 mmHg) despite optimal medical therapy.
- Patients with MS and atrial fibrillation (AF) or prior cerebrovascular event should be anticoagulated during pregnancy for prevention of embolic events
- AF is often poorly tolerated and may require cardioversion to sinus rhythm during pregnancy

Aortic stenosis:
- Etiology: most commonly bicuspid/unicuspid valves
- Severe, asymptomatic AS can be well tolerated in pregnancy but women should be followed closely in pregnancy. Consider pre-pregnancy exercise testing when possible to confirm asymptomatic state.

Patients with symptomatic AS or left ventricular systolic dysfunction preconception should be intervened upon prior to pregnancy
- Severe symptomatic AS: consider balloon valvulplasty during pregnancy if symptomatic despite medical therapy for temporary relief of obstruction during pregnancy; definitive therapy can then be deferred to post-partum. TAVR during pregnancy has been utilized in case reports.
- Aortic imaging should be obtained pre-conception (or early pregnancy when not evaluated pre-conception) in patients with bicuspid disease to evaluate for presence of aortic pathology

Significant mitral, aortic, or tricuspid regurgitation:
- Etiology: most commonly rheumatic, mitral valve prolapse, bicuspid aortic disease, Ebstein anomaly (tricuspid regurgitation) or a sequela of endocarditis
- Diuretic therapy for symptomatic patients
  - Due to decrease in SVR during pregnancy, regurgitant lesions are often well tolerated
  - After delivery, SVR suddenly increases and total body volume remains high: as such, patients may be at greatest risk for heart failure in the early post-delivery period

Pulmonary regurgitation
- Etiology: most commonly the result of tetralogy of Fallot repair
- Right ventricular function and/or branch pulmonary artery stenosis increase the risk of adverse events, most commonly right-sided heart failure

Pulmonary stenosis
- Etiology: most commonly congenital
- Even severe stenosis is usually well-tolerated during pregnancy

AS aortic stenosis, *BAV* balloon aortic valvuloplasty, *PASP* pulmonary artery systolic pressure, *SVR* systemic vascular resistance

4–6 h (with normal partial thromboplastin time) and 24 h for low molecular weight heparin prior to administering neuroaxial anesthesia [51]
- If labor initiates while still therapeutically anticoagulated on warfarin, a Caesarian section should be performed due to the risk of fetal hemorrhage with vaginal delivery [41, 42]
- The **2014 AHA/ACC guidelines** recommend the addition of aspirin during the second and third trimesters [52]

– Per **2014 AHA/ACC Valvular Heart disease guidelines**, warfarin can be continued in the first trimester if at a stable dose ≤5 mg/day (as the teratogenic effects of coumadin are dose dependent) [52].

- If the baseline warfarin dose exceeds 5 mg/day (or patient/provider wishes to avoid warfarin during pregnancy), switch to dose-adjusted twice daily low molecular weight heparin or dose-adjusted continuous unfractionated heparin infusion in first trimester.

- Patients can be transitioned back to warfarin in the second trimester. Some centers avoid warfarin during pregnancy (even outside of the first trimester) and maintain patients on dose-adjusted low-molecular weight heparin with monitoring of peak and trough anti-Xa levels
- Patients should be transitioned from warfarin to dose-adjusted continuous unfractionated heparin prior to planned delivery, with brief anticoagulation cessation just prior to delivery
- Systemic anticoagulation should be re-initiated (with unfractionated heparin bridging when needed) as soon as possible after delivery
- Use of low molecular weight heparin during pregnancy requires frequent monitoring and dose-adjustment as the volume of distribution and renal clearance, significantly change during pregnancy. Published recommendations on the management of low molecular weight heparin in pregnancy recommend weekly anti-factor Xa peak and consideration of measuring trough low molecular weight heparin levels to guide dose adjustment [42, 53]
- Patients are at highest risk for adverse events when transitioning between anticoagulants or if inadequately monitored and dose-adjusted throughout pregnancy

Pregnancy-associated myocardial infarction:

- Pregnant and peripartum women are at greater risk for MI than non-pregnant women of similar age [54].
- Mechanisms of pregnancy-associated MI include SCAD, atherosclerosis, coronary thrombosis (particularly in the context of the hypercoagulable state of pregnancy), coronary artery spasm, and takotsubo cardiomyopathy
- While the absolute incidence of pregnancy-associated MI is low, resulting maternal mortality is high [55]
- An elevated troponin in a pregnant or peripartum woman always requires further investigation into CV pathology
- Most pregnancy-associated MI occurs in late pregnancy/early post-partum [56]
- Pregnancy-associated SCAD most commonly presents in the first postpartum month and with higher-risk features and poorer outcomes than non-pregnancy associated SCAD [57].
- Early angiography remains the standard of care in pregnant women presenting with ACS, with radiation reduction techniques. However, interventionalists should be aware of the possibility of pregnancy-associated SCAD given the risks with vessel fragility and given that the preferred treatment for SCAD in the stable patient is medical management. When intervention is required, choice of stent (DES versus BMS) requires multidisciplinary discussion with the Maternal-Fetal Medicine and OB anesthesia teams, particularly as there is limited data regarding P2Y12 inhibitor use during pregnancy and clopidogrel must be held for 7 days prior to epidural anesthesia [42].
- Subsequent pregnancy following pregnancy-associated MI requires counseling regarding potential risks.
  - Pregnancy is discouraged in women with prior SCAD, though based on limited data [12]

Peri-partum cardiomyopathy (PPCM):

- Defined as the development of LV systolic dysfunction (LVEF < 45%) between the last month of gestation and 5 months postpartum in the absence of another identifiable etiology [58]
- There is significant geographic variation in the disease incidence and severity for reasons that remain incompletely understood. While the incidence is ~1:3000 in the United states, it is as high as ~1:100 in parts of Africa and ~1:300 in Haiti.
- Treatment for PPCM should follow guideline recommendations for acute systolic HF due to other etiologies.

  - However, angiotensin coverting enzyme inhibitors, angiotensin receptor blockers, sacubitril/valsartan, and spironolactone are all contraindicated during pregnancy. Nitrates and hydralazine may be used when needed.
  - β-1 selective blockers can be utilized as maternal benefits significantly outweigh the potential risk of intrauterine growth restriction
  - Loop diuretics should be used when needed for volume overload. Overdiuresis should be avoided due to potential consequences for placental perfusion.
  - Digoxin may be utilized for symptomatic benefit

- Based data from the **Investigations of Pregnancy Associated Cardiomyopathy (IPAC) Study**, risk factors for lack of left ventricular functional recovery include an LVEF < 30%, left ventricular end-diastolic dimension (LVEDD) ≥6.0 cm, black race, incident presentation after 6 weeks postpartum, and right ventricular fractional area change <35% at incident presentation. Black race and LVEDD at study entry were the strongest risk factors for lack of recovery [59, 60].
- Women with a history of PPCM should be counseled on the high risk of adverse events during subsequent pregnancy
  - Women with an LVEF that has recovered to ≥50% are at low risk for maternal mortality during subsequent pregnancy, but still at high (~20%) risk of development of heart failure or recurrent LV dysfunction [61]
  - Women with an LVEF that remains <50% prior to subsequent pregnancy are at high risk for symptomatic HF (44%), worsening systolic dysfunction, and mortality (~20%); as such, pregnancy is very high risk and should be discouraged

Arrhythmias: [41, 42]

- Arrhythmias are more common during pregnancy than during the non-pregnant state
- Patients with pacemakers should have device function (including battery life) checked pre-conception
- In patients at high risk for arrhythmia, telemetry should be considered both during labor and for at least 24 h post-partum.
- Electrical cardioversion should be performed for hemodynamically significant arrhythmias and/or those refractory to medical therapy
- Supraventricular tachycardias (SVTs) are the most common sustained arrhythmias during pregnancy
  - In the acute setting, intravenous adenosine may be used if vagal maneuvers are unsuccessful.
- Atrial fibrillation:
  - Anticoagulation should be strongly considered in all patients with an elevated risk profile.
- Ventricular tachycardia
  - Hemodynamic instability should be treated with electrical cardioversion
  - May be managed acutely with intravenous lidocaine during pregnancy (but not during delivery). Amiodarone should be avoided unless absolutely necessary due to potential fetal toxicity.

Delivery Vaginal delivery is generally preferred unless caesarian section is required for obstetric indications [41, 42]

- Use of epidural anesthesia is typically advised in patients with pre-existing CVD to blunt hemodynamic changes that result from pain during labor and delivery
- Assisted second stage can be considered for women in whom Valsalva should be minimized

- Caesarian section should be performed for women on warfarin at the time of delivery onset due to the risk of fetal hemorrhage. In addition, the **ESC guidelines** suggest that Caesarian section be considered for patients with intractable HF, significant aortopathies, and severe pulmonary hypertension.
- Invasive hemodynamic monitoring is rarely required: can be considered for patients with significant pulmonary hypertension [42]

Interventions during pregnancy [42]:

- Coronary angiography should be offered to all women during pregnancy in the setting of suspected ACS given the high risk of morbidity and mortality with pregnancy-associated MI.
- Radiation reduction strategies should be utilized
- Catheter-based valvular interventions can be considered in symptomatic pregnant patients refractory to medical therapy, though the experience with this is limited
  - When possible, radiation exposure should be delayed until >12–16 weeks of gestation
- Cardiac surgery requiring cardiopulmonary bypass should be avoided unless necessary for the life of the mother given high risk of fetal morbidity and mortality (20–30%) [45]

Cardiopulmonary resuscitation during pregnancy [62]:

- Modification to standard resuscitation guidelines for non-pregnant patients include:
  - OB should be called to all codes on pregnant women in addition to the standard code team
  - Continuous manual left uterine displacement should be performed to alleviate aorto-caval compression
  - If resuscitation efforts are ongoing at 4 min, immediate cesarean delivery should be performed during ongoing resuscitation

Review questions:

1. A 68-year-old woman presents with shortness of breath and lower extremity edema. Transthoracic echocardiogram is performed and reveals dilated LV dimensions, LVEF 30%, mild MR, and moderate TR. ECG shows sinus rhythm at a heart rate of 70 bpm with an interventricular conduction delay (QRS 126 ms). She is started on lasix, carvedilol, enalapril, and spironolactone. She initially feels well, but 3 months later, she returns to clinic with exertional fatigue. What is the next step in management?
   A: Add hydralazine and isosorbide dinitrate
   B: Placement of an ICD
   C: Placement of a CRT-D
   D: Add ivabradine

Answer: C. This woman is presenting with heart failure with reduced ejection fraction, likely from a dilated cardiomyopathy. She is started on guideline-directed heart failure therapy including ß-blocker, ACE inhibitor/ARB, and an aldosterone antagonist. She warrants an ICD for primary prevention given LVEF < 35%. In addition, women are known to derive superior benefit from cardiac resynchronization therapy (CRT) than men, and at narrower QRS durations (120–129 ms). As such, she would be an excellent candidate for a CRT-D placement.

2. A 32 year-old woman with Marfan's syndrome presents to the office for routine cardiovascular follow-up. On her most recent echocardiogram 3 months ago, her maximal ascending aortic diameter was 4.6 cm with normal biventricular function and without significant valvular disease. When you ask about her thoughts regarding pregnancy, she mentions that she has been trying to conceive. She has never been pregnant before nor does she have a history of aortic dissection. The following is true regarding her next steps in management:
   A: An echocardiogram should be repeated at this time to ensure stability of her maximal ascending aortic dimension prior to pregnancy
   B: She should be monitored during pregnancy each month with an echocardiogram to ensure stability of her ascending aortic dimensions
   C: You should advise her against pregnancy at the time
   D: She should be delivered by caesarian section

Answer: C

Patients with Marfan's syndrome and ascending aortic dilation exceeding 4.5 cm are at high risk for aortic dissection during pregnancy (mWHO class IV, see Table 7-1) and should undergo elective aortic repair prior to consideration of pregnancy. Even after aortic

repair, patients should be counseled regarding the risk of aortic dissection, and beta blockers should be considered during pregnancy. While patients with ascending aortic aneurysms should undergo aortic imaging prior to pregnancy and be monitored with monthly or bimonthly echocardiograms, this patient already meets criteria for pre-pregnancy aortic repair and thus choices A and B are incorrect. While caesarian section should be considered for patients with Marfan's syndrome and aortic dimensions exceeding 4.0 cm—as well as those with acute and chronic dissections—this patient would be better managed with preconception repair given her current high risk of aortic dissection during pregnancy.

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CHAPTER 8

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Stress Testing and Cardiopulmonary Exercise Testing

CHAPTER OUTLINE

EXERCISE PHYSIOLOGY FOR THE CLINICIAN

Overview

- The cardiorespiratory or cardiopulmonary system is a group of organs responsible for the transfer of oxygen (O_2) and carbon dioxide (CO_2) between the atmosphere and the mitochondria throughout the body [1].
- Within the mitochondria, O_2 facilitates the breakdown of fundamental fuel sources (carbohydrates, fats, and proteins) into adenosine triphosphate (ATP), CO_2, water and heat.
- ATP serves as the primary energy source for most cellular processes including contraction of the skeletal and cardiac sarcomeres.
- The key organs comprising the cardiopulmonary system are the *heart, lungs, systemic and pulmonary vasculature, and hematopoietic system (red blood cells)*. Pathology within

any of these key organs will impair metabolic gas exchange and ultimately lead to clinical manifestations of cardiopulmonary disease.

- Any process that impairs either the flux of oxygen from the atmosphere to the mitochondria or the return of CO_2 from the mitochondria to the atmosphere will impair human performance and limit functional capacity.

Quantification of Work

- There is a **direct relationship between exercise intensity (external work) and the body's demand for oxygen with increasing oxygen demand being met by increasing pulmonary oxygen uptake (VO_2)**. For example, VO_2 increases directly with the power output of working muscles by approximately 10 mL O_2/min/W above baseline exertion.
- **External work** is quantifiable based on the exercise modality employed for exercise testing in units such as velocity and incline (treadmill) or watts (bicycle and rowing ergometer). Quantification of external work is required for the development and application of standardized exercise testing protocols.
- **Peak oxygen consumption** (Peak VO_2 or VO_{2max}), a metric commonly measured in clinical practice, is defined as the amount of oxygen uptake/utilization that occurs at an individual's peak level of exercise and represents the gold standard integrated measure of internal work.
- VO_2 can be measured during exercise testing (see section "Metabolic Gas Exchange Measurement") or estimated from predictive algorithms, which typically convert VO_2 into **metabolic equivalents** (METS). One MET, the average amount of energy consumed under resting conditions, is equivalent to 3.5 mL/kg/O_2.
- The cardiovascular system is responsible for transporting oxygen-rich blood from the lungs to the skeletal muscles, a process that is quantified as cardiac output (liters per minute).
- The **Fick equation** [VO_2 = *cardiac output x (Δ arterial-venous* O_2)] can be used to quantify the relationship between cardiac output and VO_2. In the healthy human, there is a direct, linear, and inviolate relationship between VO_2 and cardiac output.
- Cardiac output, the product of stroke volume and heart rate, may increase five- to sixfold during maximal exercise effort. Coordinated autonomic nervous system function, characterized by rapid and sustained parasympathetic withdrawal coupled with sympathetic activation, is required for this to occur.
- Heart rates may range from <40 beats per minute at rest to >200 beats per minute in a young, maximally exercising athlete. **Heart rate increase is responsible for the majority of cardiac output augmentation during exercise**. Maximal heart rate varies innately among individuals, decreases with age, and does not increase with exercise training.
- Stroke volume is defined as the quantity of blood ejected from the heart during each contraction. Stroke volume rises during exercise as a result of increases in ventricular end-diastolic volume (increased preload) and, to a lesser degree, sympathetically medicated reduction in end-systolic volume (increased inotropy). Cardiac chamber enlargement and the accompanying ability to generate a large stroke volume are direct results of exercise training and are the cardiovascular hallmarks of the endurance-trained athlete.
- **Cardiac limitations to exercise** are most commonly explained by failure to augment cardiac output via inadequate heart rate augmentation (chronotropic incompetence) and/or inadequate stroke volume augmentation (inotropic or lusitropic incompetence, terms that refer to inadequate cardiac muscle contraction and relaxation respectively).

EXERCISE STRESS TESTING

Overview

- **Exercise testing is used clinically to evaluate function of the cardiopulmonary system in an attempt to diagnose underlying cardiovascular or pulmonary disease, assess etiology of cardinal symptoms (chest pain, exertional dyspnea, exercise/func-**

tional intolerance) of cardiovascular or pulmonary disease, assess response to therapeutic interventions, and to determine clinical prognosis.

- Exercise testing can be performed using various exercise modalities including walking/running (treadmill), cycling (up-right or recumbent cycle ergometers), rowing (rowing ergometers), or arms only activity (arm-hand ergometers).
- **Modality selection** is typically based on institutional preferences and/or the specific goals of exercise testing as determined by the ordering clinician and their patient. The vast majority of clinical exercise testing is performed using treadmills with simultaneous use of continuous 12-lead electrocardiography (ECG) for the assessment of coronary artery disease (CAD).
- The reported rate of serious **complications during laboratory based exercise stress testing** are rare (overall ~1/10,000) with estimates of arrhythmia requiring hospitalization, acute myocardial infarction, and sudden death of <0.02%, 0.04%, and 0.01% respectively [2].

Treadmill Protocols

- Comprehensive standards for laboratory-based exercise testing which delineate facility requirements, optimal staffing, and emergency action protocols have been provided by the American Heart Association [3].
- The standard **Bruce Protocol**, designed by Seattle, Washington, USA-based pediatrician Robert A. Bruce in 1963, is the most commonly applied treadmill exercise protocol [4].
- The Standard Bruce Protocol consists of sequential 3 min stages characterized by increasing intensity as dictated by changes in treadmill incline and belt speed. Estimates of energy expenditure for each stage permit estimation of functional capacity (Table 8-1).
- The Standard Bruce Protocol is a relatively high intensity protocol and may not be optimal for truly sedentary people or patients with advanced cardiovascular disease. Alternative options in such cases include the "Modified" Bruce and Naughton Protocols.
- Absolute and relative indications for **termination of an exercise treadmill test**, as delineated by current ACC/AHA practice guidelines, are shown in Table 8-2.
- In the absence of a clinical reason for premature treadmill testing termination, all exercise treadmill tests should term0inate when the patient reaches **peak volitional exercise intensity** rather than some predefined "diagnostic" heart rate or exercise intensity.

Indications for Exercise Testing

- Clinical indications for exercise testing include the following:
  - Evaluation of symptoms suggestive of angina in patients w/o CAD history
  - Evaluation of new or worsening symptoms in patients with known CAD
  - Post-MI risk stratification
  - Evaluation of suspected arrhythmias
  - Evaluation of the severity of valvular heart disease/congenital disease
  - Disability evaluation
  - Screening in high risk populations

TABLE 8-1

STANDARD BRUCE TREADMILL PROTOCOL

STAGE	MINUTES FROM START	SPEED (M.P.H.)	INCLINE (%)	ESTIMATED METS
1	3	1.7	10	4.6
2	6	2.5	12	7.9
3	9	3.4	14	10.2
4	12	4.2	16	13.5
5	15	5.0	18	14.9
6	18	5.5	20	17.0
7	21	6.0	22	19.3

TABLE 8-2

INDICATIONS FOR TERMINATION OF EXERCISE TESTING

Absolute indications
■ Drop in systolic BP of >10 mmHg from baseline BP despite an increase in workload, when accompanied by other evidence of ischemia
■ Moderate to severe angina
■ Increasing nervous system symptoms (e.g., ataxia, dizziness, or near-syncope)
■ Signs of poor perfusion (cyanosis or pallor)
■ Technical difficulties in monitoring ECG or systolic BP
■ Subject's desire to stop
■ Sustained ventricular tachycardia
■ ST elevation (≥1.0 mm) in leads without diagnostic Q-waves (other than in leads V1 or aVR)
Relative indications
■ Drop in systolic BP of (≥10 mmHg from baseline BP despite an increase in workload, in the absence of other evidence of ischemia
■ ST or QRS changes such as excessive ST depression (>2 mm of horizontal or down-sloping ST-segment depression) or marked axis shift
■ Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias
■ Fatigue, shortness of breath, wheezing, leg cramps, or claudication
■ Development of bundle-branch block or IVCD that cannot be distinguished from ventricular tachycardia
■ Increasing chest pain
■ Hypertensive response systolic BP of >250 mmHg and/or a diastolic BP of >115 mmHg.

Modified from Gibbons et al. ACC/AHA 2002 Guideline Update for Exercise Testing [6]
ECG electrocardiogram, *PVCs* premature ventricular contractions, *IVCD* intraventricular conduction

TABLE 8-3

PRETEST PROBABILITY OF CORONARY ARTERY DISEASE AS DEFINED BY AGE, GENDER, AND SYMPTOMS

AGE (YEARS)	GENDER	TYPICAL/ DEFINITE ANGINA PECTORIS	ATYPICAL/ PROBABLE ANGINA PECTORIS	NON-ANGINAL CHEST PAIN	ASYMPTOMATIC
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	Intermediate	Intermediate	Intermediate	Low
	Women	High	Low	Very low	Very low
50–59	Men	Intermediate	Intermediate	Intermediate	Low
	Women	High	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

High = >90%; intermediate = 10–90%; low = <10%; and very low = <5%
Insufficient data exist for patients <30 or >69 years
Adopted from Diamond GA, Forrester JS. N Engl J Med 1979 [5]

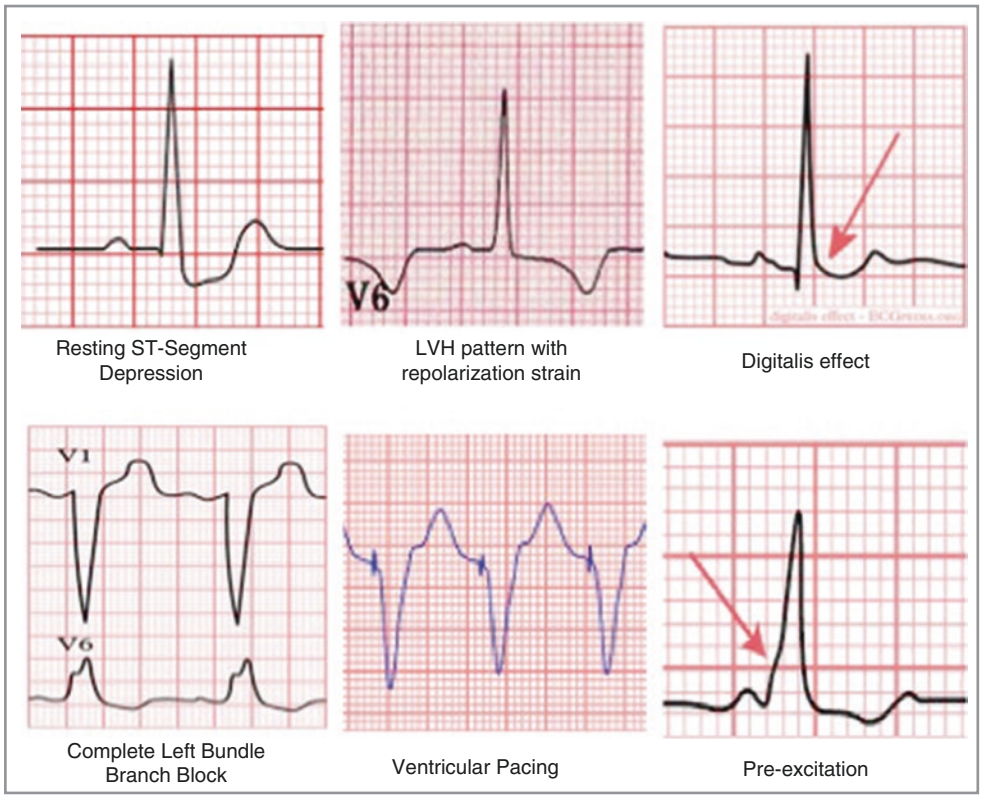
Diagnostic Considerations

- The majority of exercise treadmill testing is performed to evaluate symptoms of established or suspected CAD.
- The diagnostic utility of exercise treadmill testing coupled with continuous 12-lead ECG for CAD is dependent on the **pretest probability of disease** as dictated by age, gender, and the characteristics of presenting symptoms (Table 8-3) [5].

- **Intermediate pretest probability patients** represent ideal candidates for exercise treadmill testing. Indications for exercise testing to diagnoses obstructive CAD as delineated by current ACC/AHA guidelines are as follows [6]:
  - **Class I**
    1. Adult patients (including those with complete right bundle-branch block or less than 1 mm of resting ST depression) with an intermediate pretest probability of CAD on the basis of gender, age, and symptoms.
  - **Class IIa**
    1. Patients with vasospastic angina.
  - **Class IIb**
    1. Patients with a high pretest probability of CAD by age, symptoms, and gender.
    2. Patients with a low pretest probability of CAD by age, symptoms, and gender.
    3. Patients with less than 1 mm of baseline ST depression and taking digoxin.
    4. Patients with electrocardiographic criteria for left ventricular hypertrophy (LVH) and less than 1 mm of baseline ST depression.
  - **Class III**
    1. Patients with the following baseline ECG abnormalities: Pre-excitation (Wolff-Parkinson-White) syndrome, electronically paced ventricular rhythm, greater than 1 mm of resting ST depression, and/or complete left bundle-branch block
    2. Patients with a documented myocardial infarction or prior coronary angiography demonstrating significant disease have an established diagnosis of CAD. However, ischemia and risk can be determined by testing.
  - **ST-Segment Interpretation Considerations**
    - **Dynamic ST-segment** depression (≥1 mm in at least two consecutive leads) with horizontal or down-sloping contour, as assessed 60–80 ms after the terminal QRS j-point, represents the most specific finding for underlying obstructive CAD. However, the location of the ST-segment depressions does not help localize the ischemia/obstructive lesions.
    - **ST-segment depression in lead V5** represents the most specific lead for underlying obstructive CAD. ST-segment depression isolated to the inferior limb leads (II, III, and aVF) has comparatively poor accuracy for underlying disease and should not be relied on.
    - Dynamic **up-sloping ST-segment depression** has inadequate diagnostic accuracy to establish the presence of underlying obstructive CAD but its presence does not exclude obstructive CAD.
    - **Dynamic ST-segment elevation** in the absence of Q-waves is: (1) highly suggestive of transmural ischemia, (2) indicative of arrhythmic instability, and (3) an accurate localizer of ischemic myocardium. In the presence of Q-waves, ST-segment elevation typically indicates a previously infarcted aneurysmal segment of ventricular myocardium.
    - There are **six resting ECG patterns that definitively reduce the diagnostic accuracy of the exercise ECG**, both by decreasing sensitivity and specificity, for the diagnosis of obstructive CAD. These include digoxin effect, left ventricular hypertrophy with repolarization changes, ventricular pre-excitation, complete left bundle branch block, resting ST-segment depression (>1 mm), and electronically paced ventricular rhythms (Fig. 8-1).

FIGURE 8-1

Resting ECG patterns associated with reduced diagnostic accuracy for the assessment of suspect obstructive CAD during exercise stress testing



Absolute Contraindications for Exercise Testing

- Absolute contraindications to the initiation of exercise testing include the following:
  - Acute myocardial infarction attributable to an acute coronary syndrome (within 2 days)
  - High-risk unstable angina
  - Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
  - Symptomatic severe aortic stenosis
  - Uncontrolled symptomatic heart failure
  - Acute pulmonary embolus or pulmonary infarction
  - Acute myocarditis or pericarditis
  - Acute aortic dissection

Relative Contraindications for Exercise Testing

- Relative contraindications to the initiation of exercise testing, which may be superseded if the benefits of testing out-weigh the risks, include the following:
  - Known left main coronary stenosis
  - Moderately stenotic valvular heart disease
  - Electrolyte abnormalities
  - Severe arterial hypertension
  - Tachyarrhythmias or bradyarrhythmias
  - Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
  - Mental or physical impairment leading to inability to exercise adequately
  - High-degree atrioventricular block defined as either Type II second degree or third degree block

Prognostic Assessment

- Among patients with suspected or known CAD, data derived from exercise testing provides valuable information that can be used to **manage clinical decision-making and to estimate prognosis.**
- Testing to volitional fatigue permits determination of **peak exercise capacity**, a powerfully prognostic marker, that can quantified by numerous metrics including:
  - Maximum exercise work load
  - Maximum exercise duration
  - Maximum estimated MET level achieved
- Electrocardiographic markers that indirectly reflect the extent of **inducible ischemia** and that have established prognostic significance include:
  - Depth and contour of exercise-induced ST-segment depression
  - Number of leads with ST-segment elevation (in leads without pathological Q waves) under resting conditions
  - Reproduction of exercise-induced angina
- The following **hemodynamic data** which can be obtained during exercise testing also contains prognostic data which can identify high risk coronary disease patients:
  - Maximum heart rate <80% age/gender predicted maximum [7].
  - Blunted maximum exercise systolic blood pressure (BP) defined as augmentation of <30 mmHg above resting pressure [8].
  - 2-min post exercise heart rate recovery ≤12 beats/min [9].
  - Maximum exercise double product (peak heart rate × peak systolic BP) [10].
- **Scoring tools** that integrate exercise capacity, electrocardiographic data, and hemodynamic data are in widespread clinical use. The Duke Treadmill Score (DTS) is the most commonly employed tool and is calculated using the following formula [11]:
  - DTS = exercise time – 5×(ST-segment depression)−4×(angina index)
  - ST-segment depression is maximal depth, measured in millimeters, at 60–80 ms past the QRS J-point.
  - Angina index values: 0 = no angina, 1= angina occurred, 2 = angina occurred and was the reason the patient ceased exercising.

ADJUNCTIVE TESTING: CARDIAC IMAGING

Overview

- Cardiac imaging should be paired with exercise testing for the assessment suspected CAD in specific patient groups in which the exercise electrocardiogram is known to have unacceptable diagnostic accuracy.
- Cardiac imaging can be paired with exercise testing in patients with confirmed CAD for the purposes of localizing ischemia, documenting the extent of ischemia, assessing ventricular function, and determining tissue viability following myocardial infarction.
- Cardiac imaging must be used in all forms of pharmacologic stress including vasodilator testing and inotropic/chronotropic stimulation.
- The major categories of cardiac imaging for use in the assessment of suspected or confirmed CAD are: (1) myocardial perfusion imaging and (2) transthoracic echocardiography

Types of Cardiac Imaging

- Clinically available cardiac imaging options, for use in conjunction with either exercise stress testing or pharmacological stress testing, include nuclear myocardial perfusion imaging (MPI) agents and direct visualization using echocardiography or tomographic imaging with cardiac magnetic resonance imaging or computed tomography.
- **Nuclear MPI agents** can be divided into agents that require single-photon emission computed tomography (SPECT) versus those that require positron emission tomography (PET).
- The diagnosis and quantification of CAD using nuclear MPI relies on perfusion heterogeneity with diseased territories receiving less blood flow and thus less tracer uptake.
- Most commonly used SPECT imaging nuclear MPI agents include thallium-201 and technicium-99m labelled sestamibi (Cardiolite™) and tetrofesmin (Myoview™) [12]. Both tracers require two imaging phases following both a "resting" and a "stress" injection of tracer [13]:
  - Thallium-201:
    - Potassium analog utilizing active membrane transport into myocytes
    - Freely exchanged after initial uptake ("washout")
    - Long half life (~73 h)
    - High first-pass myocardial extraction coefficient (85%)
    - Cleared by urinary excretion
    - Nuclear MPI of choice for myocardial viability assessment
    - The dose of ionizing radiation ranges from approximately 11–24 mSv depending on the protocol used [11].
  - Technicium labeled MPI's:
    - Cationic tracer that freely diffuses into myocytes without active uptake
    - Near permanent sequestration in myocyte mitochondrial after uptake
    - Short half life (~6 h)
    - Intermediate first-pass myocardial extraction coefficient (50–70%)
    - Hepatobiliary clearance
    - Nuclear MPI of choice for assessment of left ventricular function
    - The dose of ionizing radiation ranges from approximately 4–16 mSv depending on the protocol used [11].
- **PET stress imaging** relying on various tracers including ^{15}O water, ^{13}N ammonium, and ^{82}Rubidium are increasingly being used as alternatives to SPECT nuclear MPI. Advantages of PET over SPECT MPI, include inherent attenuation correction and superior temporal and spatial resolution. Thus, PET may outperform SPECT in female patients with abundant breast tissue and among obese patients of both genders. Cost and technical complexity currently limit PET stress MPI to tertiary care medical centers.
- **Transthoracic echocardiography and cardiac magnetic resonance imaging provide alternatives to nuclear MPI**.
- Properties of transthoracic echocardiography include the following:
  - No exposure to radiation
  - Suitable for use in conjunction with exercise. Imaging can be performed during supine semi-recumbent cycle exercise or immediately following treadmill exercise
  - Suitable for use in conjunction with pharmacologic stress with dobutamine. Imaging can be performed during escalating dose dobutamine infusion
  - Diagnosis of CAD suggested by direct visualization of resting (old infarction) or dynamic (ischemic territory) wall motion defects
  - Exercise or pharmacologic stress echocardiography is preferred diagnostic modality of choice for the assessment of suspected CAD in patients with LBBB on resting 12-lead ECG.
  - Highly operator and patient body habitus dependent

- Properties of cardiac magnetic resonance imaging stress include the following:
  - Superior spatial resolution to transthoracic echocardiography
  - More costly and time consuming than transthoracic echocardiography.
  - Currently only i.n clinical use in conjunction with pharmacologic stress testing.

Indications for Cardiac Imaging

- Among patients presenting with suspected CAD who are **capable** of exercise, exercise ECG with cardiac imaging is indicated as follows [14]:
  - **Class 1:**
    - Exercise stress with cardiac imaging is recommended for patients with an intermediate to high pretest probability of CAD who have an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity.
  - **Class 2b:**
    - For patients with a low pretest probability of obstructive CAD who do require testing, standard exercise stress echocardiography might be reasonable, provided the patient has an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity
  - **Class 3:**
    - Pharmacological stress with cardiac imaging is not recommended for patients who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.
    - Exercise stress with cardiac imaging is not recommended as an initial test in low-risk patients who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.
- Among patients presenting with suspected CAD who are **unable** to exercise, exercise ECG with cardiac imaging is indicated as follows [14]:
  - **Class 1:**
    - Pharmacological stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of CAD who are incapable of at least moderate physical functioning or have disabling comorbidity.
  - **Class 2a:**
    - Pharmacological stress echocardiography is reasonable for patients with a low pretest probability of CAD who require testing and are incapable of at least moderate physical functioning or have disabling comorbidity.
  - **Class 3:**
    - Standard exercise ECG testing is not recommended for patients who have an uninterpretable ECG or are incapable of at least moderate physical functioning or have disabling comorbidity.
- Among patients presenting with known CAD who are **capable** of exercise, exercise ECG with cardiac imaging is indicated as follows [14]:
  - **Class 1:**
    - The addition of either nuclear MPI or echocardiography to standard exercise ECG testing is recommended for risk assessment in patients with known CAD who are able to exercise to an adequate workload but have an uninterpretable ECG not due to left bundle branch block or ventricular pacing

  - **Class 2a:**
    - The addition of either nuclear MPI or echocardiography to standard exercise ECG testing is reasonable for risk assessment in patients with known CAD who are able to exercise to an adequate workload and have an interpretable ECG
  - **Class 3:**
    - Pharmacological stress imaging (nuclear MPI, echocardiography, or CMR) is not recommended for risk assessment in patients with known CAD who are able to exercise to an adequate workload and have an interpretable ECG.
- Among patients presenting with known CAD who are **unable** to exercise, exercise ECG with cardiac imaging is indicated as follows [14]:
  - **Class 1:**
    - Pharmacological stress with either nuclear MPI or echocardiography is recommended for risk assessment in patients with stable CAD who are unable to exercise to an adequate workload regardless of interpretability of ECG
- Regardless of a patient's exercise capacity, cardiac imaging (either nuclear MPI or echocardiography) in conjunction with pharmacologic stress testing, is indicated for risk assessment in patients with known CAD and left bundle branch block on the resting ECG (Class 1).
- Regardless of a patient's exercise capacity, cardiac imaging (either nuclear MPI or echocardiography) in conjunction with either exercise stress or pharmacologic stress testing (as dictated by exercise capacity) is recommended in patients who are undergoing consideration for revascularization of a known coronary stenosis of unclear physiological significance (Class 1).

PHARMACOLOGIC STRESS TESTING

Overview

- Patients with suspected or known CAD that require stress testing but that are **unable to exercise to moderate or high intensity workloads** due to musculoskeletal limitations or concomitant non-cardiovascular disease require an alternative in the form of pharmacological stress testing.
- Pharmacological stress with cardiac imaging is **not recommended for patients who have an interpretable ECG and at least moderate physical functioning** or no disabling comorbidity (Class 3).
- Pharmacologic stress testing can be performed using continuous infusion of **vasodilators or inotropic agents** in conjunction with cardiac imaging.

Vasodilator Pharmacologic Stress Testing

- There are currently three coronary vasodilators available for clinical use: adenosine, dipyridamole, and regadenason.
- Vasodilators must be used in conjunction with nuclear MPI imaging.
- The use of vasodilators to diagnoses CAD relies on heterogeneous dilation of the coronary artery system characterized by relatively impaired dilation of diseased arteries and thus comparatively less delivery of MPI compared to healthy arteries.
- **Multi-vessel disease** may fail to produce such heterogeneity and is an important cause of false negative vasodilator MPI testing.
- Key properties of the commercially available vasodilators include [12]:

- **Adenosine**
  - Mechanism of Action: coronary vasodilation via activation of the A_{2A} receptor.
  - Activation of alternative A receptors responsible for many common undesirable side effects including: flushing (35–40%), chest pain (25–30%), dyspnea (20%), transient AV node block (8%), dizziness (7%), nausea (5%), and symptomatic hypotension (5%)
  - Half life ~ 10 min
  - Testing should be done >3 h after food ingestion and >12 h after ingestion of any products containing methylxanthines (i.e. caffeine).
  - MPI tracer injection typically given mid-way through 6-min adenosine infusion.
  - Absolute contraindications to adenosine include:
    - Patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease as defined by the need for corticosteroid-based therapy and/or history of acute exacerbation requiring hospitalization
    - Second- or third-degree AV block without a functioning pacemaker.
    - Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia, without a functioning pacemaker.
    - Systolic BP < 90 mmHg.
    - Pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency.
    - Uncontrolled hypertension (systolic BP > 200 mmHg or diastolic BP > 110 mmHg).
    - Recent (<48 h) use of dipyridamole or dipyridamole-containing medications (e.g., Aggrenox).
- **Dipyridamole**
  - Mechanism of Action: Indirect coronary vasodilation by inhibiting intracellular reuptake and deamination of adenosine.
  - Half life ~ 35–40 min
  - Common side effects include: chest pain (20%), headache (12%), dizziness (12%), ventricular extra-systoles (5%), nausea (5%), symptomatic hypotension (5%), and flushing (5%).
  - MPI tracer injection typically given 3–5 min after dipyridamole infusion.
  - Absolute contraindications to dipyridamole include:
    - Patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease
    - Systolic BP < 90 mmHg
    - Uncontrolled hypertension (systolic BP > 200 mmHg or diastolic BP > 110 mmHg)
    - Ingestion of caffeinated foods or beverages (e.g., coffee, tea, sodas) within the last 12 h
    - Known hypersensitivity to dipyridamole
    - Unstable angina, acute coronary syndrome, or less than 2–4 days after an acute myocardial infarction
- **Regadenason**
  - Mechanism of Action: high affinity agonist for A_{2A} receptor.
  - Half life ~ 2–4 min for key pharmacodynamics phase of action
  - Common side effects include: headache (29%), rhythm or conduction abnormalities (26%), dyspnea (25%), flushing (17%), chest discomfort (11%), chest pain (8%), angina (8%), dizziness (7%), nausea (6%), and abdominal discomfort (6%).
  - MPI tracer injection typically given 10–20 s after 10 s IV push infusion of regadenason.
  - Absolute contraindications to regadenason include:

  - Patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease
  - Second- or third-degree AV block without a functioning pacemaker
  - Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia, without a functioning pacemaker
  - Systolic BP < 90 mmHg
  - Uncontrolled hypertension (systolic BP > 200 mmHg or diastolic BP > 110 mmHg)
  - Known hypersensitivity to regadenason
  - Unstable angina, acute coronary syndrome, or less than 2–4 days after an acute myocardial infarction

- All three vasodilators can be used in conjunction with low-level exercise (e.g. 1.7 mph, 0% grade treadmill during infusion) to reduce side effects and improve image quality. Not recommended in patients with left bundle branch block, pre-excitation, or ventricular pacing.
- **Reversal of severe vasodilator side effects** can be accomplished via IV infusion of aminophylline (50–250 mcg) given 1–2 min after MPI tracer injection.

Inotropic/Chronotropic Stimulatory Stress Testing

- **Dobutamine** is the only clinically available synthetic catecholamine stress agent.
- Mechanism of action: direction stimulation of the beta 1 and 2 adrenergic receptors leading to an increase in heart rate, BP, and myocardial contractility similar to exercise.
- The use of dobutamine to diagnoses CAD relies on heterogeneous augmentation of the coronary artery blood flow and tissue stimulation with relatively impaired blood flow delivery and inotropic myocyte stimulation to diseased territories.
- Common side effects include: chest pain (31%), palpitations (29%), headache (14%), flushing (14%), dyspnea (14%), and significant supraventricular or ventricular arrhythmias (8–10%).
- Absolute contraindications to dobutamine include:

  - Unstable angina, acute coronary syndrome, or less than 2–4 days after an acute myocardial infarction
  - Hemodynamically significant left ventricular outflow tract obstruction.
  - Atrial tachyarrhythmias with uncontrolled ventricular response.
  - Prior history of ventricular tachycardia.
  - Uncontrolled hypertension (systolic BP > 200 mmHg or diastolic BP > 110 mmHg)
  - Patients with aortic dissection.
  - Known hypersensitivity to dobutamine.

- **Reversal of severe dobutamine side effects** can be accomplished via IV administration of a short acting beta-blocker (i.e. metoprolol 5 mg over 1 min).

Indications for Pharmacologic Testing:

- **Inability to perform adequate exercise** due to non-cardiac physical limitations (pulmonary, peripheral vascular, musculoskeletal, or mental conditions) or due to lack of motivation. Notably, as with exercise testing, anti-ischemic cardiac medications (including b-blockers, nitrates, and calcium antagonists) have been reported to decrease the diagnostic accuracy of pharmacologic stress testing.
- The presence of **baseline electrocardiographic abnormalities**: LBBB, ventricular pre-excitation (WPW syndrome), and permanent ventricular pacing.
- **Risk stratification of clinically stable patients** into low- and high-risk groups after acute myocardial infarction.
- **Diagnosis or risk stratification following presentation to the emergency department** with a presumptive acute coronary syndrome that has been excluded by serial clinical evaluation, ECGs, and serum markers.

- Dobutamine should be considered a secondary pharmacologic stressor that is recommended only in patients who cannot undergo exercise stress and who also have contraindications to pharmacologic vasodilator stressors such as bronchospastic airway disease.

METABOLIC GAS EXCHANGE MEASUREMENT

Overview

- Metabolic or ventilatory gas exchange analysis during exercise testing may be a useful adjunctive tool in the assessment of patients with known cardiac disease, pulmonary disease, or exercise impairment of unclear etiology [15].
- Gas exchange measurement involves the use of a closed loop system in which inspired oxygen and expired carbon dioxide are measured by a conventional Douglas Bag system or a more recently designed breath-by-breath rapid gas analyzer.
- Key parameters measured during metabolic or ventilatory gas exchange analysis include oxygen uptake (VO_2), carbon dioxide output (VCO_2), and minute ventilation (VE).
- Numerous calculated metrics including the ventilatory threshold, oxygen pulse, and ventilatory efficiency can be readily derived from these three principal measurements.

Key Metabolic Gas Exchange Parameters:

- **Peak VO_2**
  - **Definition:** Maximal amount of oxygen utilized at peak volitional level of exercise. Peak VO_2 is a highly integrative parameter that accounts for:
    - Oxygen uptake in the lungs (pulmonary parenchymal and vascular function)
    - Oxygen delivery from the lungs to the peripheral tissue by the cardiovascular system (heart and systemic circulatory system)
    - Oxygen extraction and utilization by the peripheral tissue (skeletal muscle and visceral organ function).
  - **Clinical Utility:** Gold standard measurement of exercise capacity. Strongly prognostic as a determinant of longevity and quality of life across numerous healthy and infirm patient populations.
- **Peak VCO_2**
  - **Definition:** Maximal amount of carbon dioxide utilized at peak volitional level of exercise. Like peak VO_2, an integrated measurement of cardio-pulmonary-skeletal muscle function.
  - **Clinical Utility:** Negligible in isolation but required for the calculation of numerous additional parameters.
- **Breathing Reserve**
  - **Definition:** Percentage of maximal voluntary ventilation at peak volitional levels of exercise. Typically 70–80% in healthy normally active adults. This parameter is commonly calculated from forced expiratory volume at 1-s ($FEV_1 \times 40$) as obtained during resting spirometry and may be prone to measurement error.
  - **Clinical Utility:** When approaching 100%, when in conjunction with a reduced peak VO_2, can be used to define a pulmonary mechanical limit to breathing.
- **Respiratory Exchange Ratio ($RER=VCO_2/VO_2$)**
  - **Definition:** Ratio of VCO_2 to VO_2 that reflects substrate utilization. An RER 1.0 indicates pure carbohydrate metabolism while an RER of <1.0 indicates a mixture of carbohydrates with fats (pure RER ~ 0.7) and proteins (pure RER ~ 0.8).

- **Clinical Utility:** An RER > 1.0 indicates concomitant metabolism of carbohydrates and lactic acid (and or hyperventilation) and is commonly used to verify a maximal effort test (cut-points of 1.05 and 1.10 are applied for this purpose based on institutional preferences.

■ **Oxygen Pulse (VO_2/HR)**

- **Definition:** Ratio of VO_2 to heart rate.
- **Clinical Utility:** Oxygen pulse patterns, in the absence of a disease process that impairs peripheral arterial oxygen extraction, can be used as a semi-quantitative indicator of stroke volume as dictated by the Fick equation.

■ **Ventilatory Threshold**

- **Definition:** Exercise intensity during graded exercise at which production of VCO_2 exceeds consumption of VO_2. The ventilatory threshold serves as a non-invasive surrogate of the lactate threshold which is the exercise intensity above which lactic acid cannot be sufficiently buffered or excreted to maintain equilibrium. Occurs at 50-60% peak VO_2 intensity in healthy, normally active people.
- **Clinical Utility:** Key determinant of submaximal exercise capacity. Commonly decreased (<40% peak VO_2 intensity) in patients with disease. Highly sensitive to exercise training and thus the most sensitive measurement to assess fitness changes as dictated by cardiac rehabilitation or exercise prescription.

■ **Ventilatory Efficiency (VE/VCO_2)**

- **Definition:** Ratio of minute ventilation (VE) to carbon dioxide production (VCO_2). This ratio physiologically reflects how much gas must be ventilated to excrete requisite carbon dioxide with normal subjects demonstrating values of <33 at the ventilatory threshold and <36 at peak exercise.
- **Clinical Utility:** An indicator or right ventricular/pulmonary vascular/pulmonary parenchymal function. Elevations of this ratio may reflect abnormalities across these organ systems and have established prognostic value in heart failure populations.

ACC/AHA Indications for Metabolic Gas Exchange Measurement

Class 1

■ Evaluation of exercise capacity and response to therapy in patients with heart failure who are being considered for heart transplantation (Table 8-4).
■ Assistance in the differentiation of cardiac versus pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain.

Class 2a

■ Evaluation of exercise capacity when indicated for medical reasons in patients in whom the estimates of exercise capacity from exercise test time or work rate are unreliable.

Class 2b

■ Evaluation of the patient's response to specific therapeutic interventions in which improvement of exercise tolerance is an important goal or end point.
■ Determination of the intensity for exercise training as part of comprehensive cardiac rehabilitation.

Class 3

■ Routine use to evaluate exercise capacity.

A summary of common clinical scenarios and corollary choice of stress testing modalities is shown in Table 8-5.

TABLE 8-4

ACC/AHA GUIDELINES FOR PEAK EXERCISE OXYGEN UPTAKE AS A CRITERION FOR CARDIAC TRANSPLANTATION

CATEGORY FOR TRANSPLANT	PEAK VO_2 (ML/KG/MIN)
Accepted indication	<10
Probable indication	<14
Inadequate indication	>15

TABLE 8-5

SUMMARY OF COMMON CLINICAL SCENARIOS DICTATING CHOICE OF STRESS TESTING MODALITY

CLINICAL SCENARIO	OPTIMAL STRESS TEST MODALITY
Diagnosis or exclusion of CAD among adult patients with an intermediate pretest probability of CAD and an "interpretable" baseline ECG	Non-imaging exercise stress test
Diagnosis or exclusion of CAD among adult patients with an intermediate to high pretest probability of CAD who have an uninterpretable ECG and/or at least moderate physical functioning or no disabling comorbidity	Exercise stress test with adjunct imaging (myocardial perfusion or echocardiography)
Diagnosis or exclusion of CAD among adult patients who are unable to exercise to moderate or high intensity workloads due to musculoskeletal limitations or concomitant non-cardiovascular disease	Pharmacologic vasodilator stress test with adjunct imaging *Note: Vasodilator agents contraindicated in the presence of a history of moderate or greater reactive airway disease (see full list of contraindications).
Diagnosis or exclusion of CAD among adult patients with an intermediate to high pretest probability of CAD who have an uninterpretable ECG due to conditions that prolong the QRS complex (LBBB, ventricular pre-excitation, and permanent ventricular pacing)	Pharmacologic vasodilator stress test with adjunct imaging
Diagnosis or exclusion of CAD among adult patients who are unable to exercise to moderate or high intensity workloads due to musculoskeletal limitations or concomitant non-cardiovascular disease in the presence of a history of moderate or greater reactive airway disease	Pharmacologic dobutamine stress test with adjunct imaging
Evaluation of exercise capacity and response to therapy in patients with heart failure who are being considered for heart transplantation	Exercise stress testing with metabolic gas exchange
Differentiation of cardiac versus pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity	Exercise stress testing with metabolic gas exchange

Review Questions:

1. A 40-year-old female presents for evaluation of chest pain. She describes "central chest pressure" that comes on when she is angry or frustrated by her students at work (she teaches fourth grade) or by her three young children and in-laws at home. The discomfort is accompanied by shortness of breath and is relieved within a few minutes by leaving stressful situations or by resting in a quiet place. She denies any chest symptoms during exercise and describes routine brisk walking during which she experiences no subjective chest pain. She has no history of diabetes or hypertension but smokes one pack of cigarettes daily and is moderately overweight. Her cholesterol has never been checked. Her father underwent CABG at age 53 and died of an MI at age 61. On physical exam, her BP is 126/70 mmHg and HR is 80 bpm and regular. Her cardiac exam is normal. Her resting ECG shows sinus rhythm with no abnormalities.

What is the preferred initial diagnostic test on this patient according to ACC/AHA practice guidelines?

a. **Exercise treadmill testing**
b. Exercise testing with myocardial perfusion imaging
c. Adenosine testing with myocardial perfusion imaging
d. Exercise echocardiography
e. Dobutamine echocardiography

2. A 65 year-old man with advanced heart failure with reduced ejection fraction is failing maximal medical therapy and is being considered for advanced therapies including cardiac transplantation and left ventricular mechanical support. He is referred for an exercise test with metabolic gas exchange to confirm his candidacy. Which of the following metrics provide independently prognostic information that can be used to support a prescription for advanced therapies?
   a. Ventilatory Efficiency (VE/VCO_2)
   b. Peak VO_2
   c. 2-min. heart rate recovery
   d. Peak work
   e. **All of the above**

3. Which of the following statements about exercise is false?
   a. The inability to perform an exercise test is a bad prognostic sign.
   b. Exercise is the stress technique preferred for use with myocardial perfusion imaging.
   c. The ability to reach or exceed four METS of exercise predicts a low-risk of cardiac events during most non-cardiac surgical procedures.
   d. Functional exercise capacity provides any additional independent prognostic information when the results of exercise MPI are taken into account.
   e. **The achievement of 85% of age-predicted maximal HR is the preferred end-point for exercise testing.**

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CHAPTER 9

KENTA NAKAMURA, RAHUL SAKHUJA, AND IK-KYUNG JANG

Cardiac Catheterization and Intervention

CHAPTER OUTLINE

ABBREVIATIONS

ACS	Acute coronary syndrome
AI	Aortic insufficiency
AP	Anterior posterior
AS	Aortic stenosis
AV	Aortic valve
AVA	Aortic valve area
BSA	Body surface area
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CIN	Contrast induced nephropathy
CTO	Chronic thrombotic occlusion
CO	Cardiac output
CVA	Cerebrovascular accident
CVP	Central venous pressure
DFP	Diastolic flow period
DM	Diabetes mellitus
FFR	Fractional flow reserve
HF	Heart failure
HOCM	Hypetrophic obstructive cardiomyopathy
HR	Heart rate
IVC	Inferior vena cava
IVUS	Intravascular ultrasound
LA	Left atrium
LAA	Left atrial appendage
LAD	Left anterior descending artery
LAP	Left atrial pressure
LAO	Left anterior oblique
LCx	Left circumflex artery
LIMA	Left internal mammary artery
LM	Left main
LVAD	Left ventricular assist device
LVEDP	Left ventricular end diastolic pressure
MAP	Mean arterial pressure

MCS	Mechanical circulatory support
MR	Mitral regurgitation
MV	Mitral valve
MVA	Mitral valve area
MVO_2	Mixed venous oxygen saturation
NSTEMI	Non-STE-elevation myocardial infarction
OCT	Optical coherence tomography
PA	Pulmonary artery
PAO_2	Pulmonary artery oxygen saturation
PAWP	Pulmonary artery wedge pressure
PBF	Pulmonary blood flow
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
PHT	Pulmonary hypertension
PVO_2	Pulmonary venous oxygen saturation
PVR	Pulmonary vascular resistance
RA	Right atrium
RAO	Right anterior oblique
RCA	Right coronary artery
RV	Right ventricle
RVEDP	Right ventricular end diastolic pressure
SAVR	Surgical aortic valve replacement
SBP	Systemic blood flow
SCD	Sudden cardiac death
SEP	Systolic ejection period
STEMI	ST-elevation myocardial infarction
SVC	Superior vena cava
SVG	Saphenous vein graft
TAVR	Transcatheter aortic valve replacement
VO_2	Oxygen consumption

CARDIAC CATHETERIZATION

- 1 million inpatient diagnostic cardiac catheterizations and 480,000 percutaneous coronary interventions (PCI) were performed in U.S. in 2014
- The number of cardiac catheterizations and PCI have **steadily decreased** over the past decade
- **Contraindications (all relative):** active gastrointestinal bleeding, coagulopathy (INR > 1.8), acute renal failure, acute aortic injury, acute stroke, untreated infection, anemia, anaphylactoid contrast allergy, intracranial hemorrhage

RADIATION SAFETY [1]

- **Deterministic effects of radiation (severity of injury related to dose):** hair loss, skin injury, cataracts (typically >5 Gy)
- **Stochastic effects (probability of injury related to dose):** cancer, genetic defects
- Typical dose of cardiac catheterization <1 Gy, with goal dose is as low "**As Low As Reasonably Achievable" (ALARA)**
- Operator exposure is predominantly from scatter from the patient's body
- Energy of radiation decreases with square root of distance (inverse square law)

ARTERIAL ACCESS

- **Femoral artery** was the traditional access of choice for left heart catheterization, but the **radial artery** is increasingly popular and is now generally considered standard of care.
- Compared to femoral artery access, radial artery access offers reduced: [2]
  - Major bleeding (relative risk of 0.57)
  - Death (relative risk of 0.73)
  - Major adverse cardiovascular events (relative risk of 0.86)
  - Time to ambulation and patient comfort
- Disadvantage of radial access includes:
  - Technically challenging
  - Potentially ↑ radiation and contrast exposure, but generally comparable total procedure time including STEMI cases
  - Up to 20% procedure failure rate and conversion to femoral access (due typically to vasospasm, tortuous anatomy, or difficult coronary engagement)
- **Ulnar access:** Increasingly recognized as alternative for radial access with comparable safety profile for experienced radial operators
- **Brachial access:** Rarely used, similar complication rate as femoral access

LEFT HEART CATHETERIZATION

- Use of anticoagulation indicated for **prolonged cases** (e.g. previous coronary artery bypass graft (CABG), when crossing stenotic aortic valve (AV) and cases using **transradial or ulnar access**)

A) **Coronary angiography (see below):**

B) **Left ventriculography** (Figs. 9-1–9-4)**:**

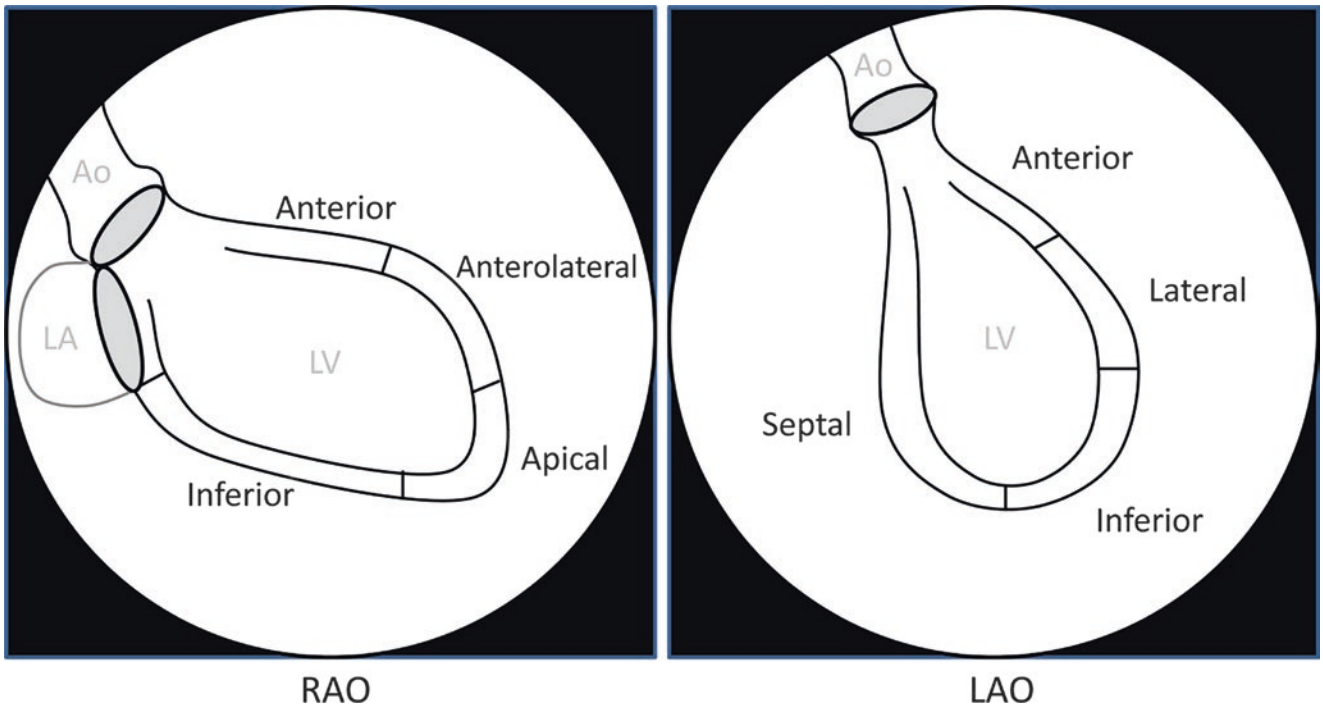


FIGURE 9-1

Left ventriculography. *Ao* aorta, *LA* left atrium, *LV* left ventricle

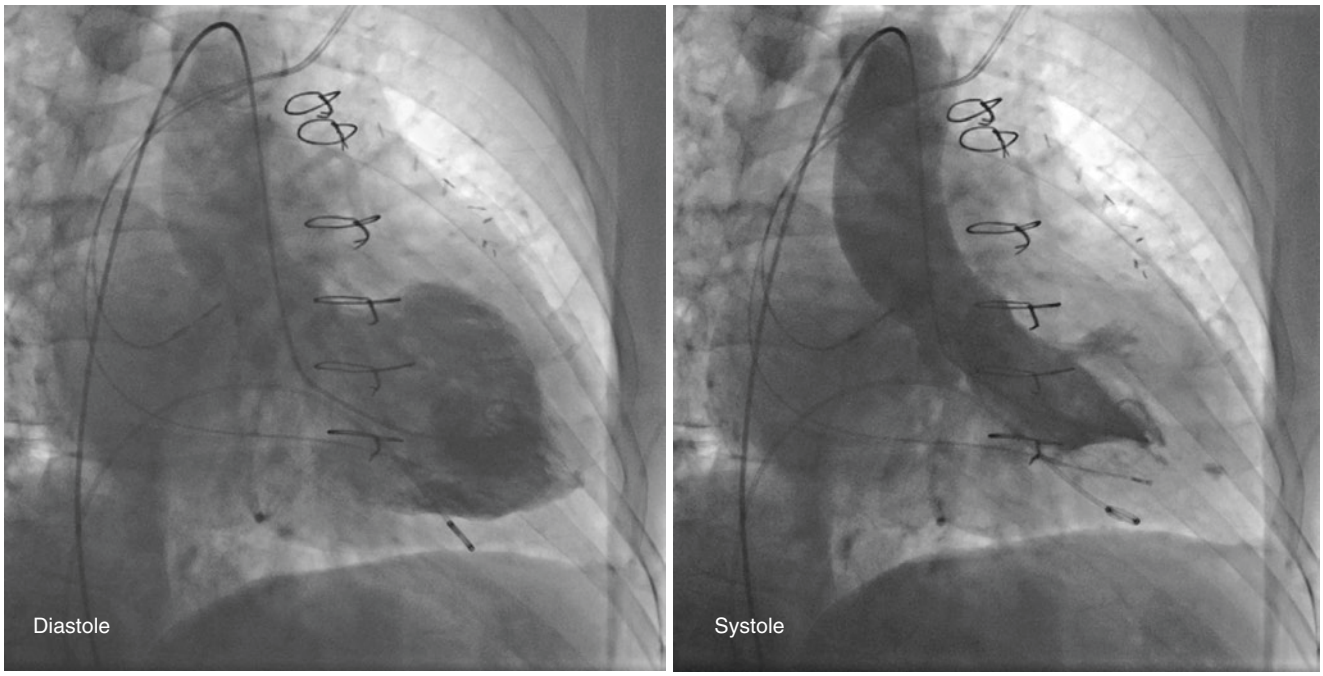
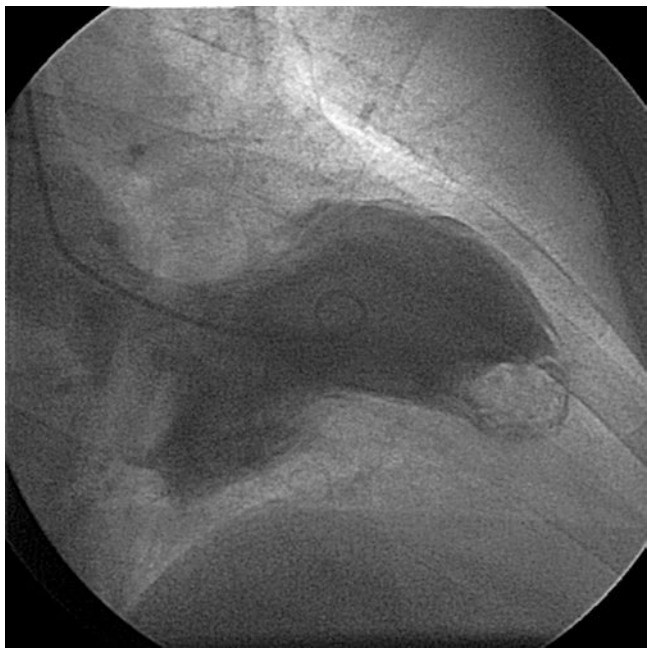


FIGURE 9-2

Apical hypertrophic cardiomyopathy in RAO projection

FIGURE 9-3

A calcified left ventricular apical thrombus in RAO projection



- Left ventriculography by power injection of 25–35 mLs of contrast at 10–15 mL/s:
  - Right anterior oblique (RAO) is the preferred projection for anterior, anterolateral, apical, and inferior walls
  - Left anterior oblique (LAO) preferred view for the inferior/posterior and septal walls
  - Left ventriculogram **contraindicated** (relative) if left ventricular end diastolic pressure (LVEDP) > 25 mmHg or in presence of critical left main coronary artery stenosis (LMCA) stenosis

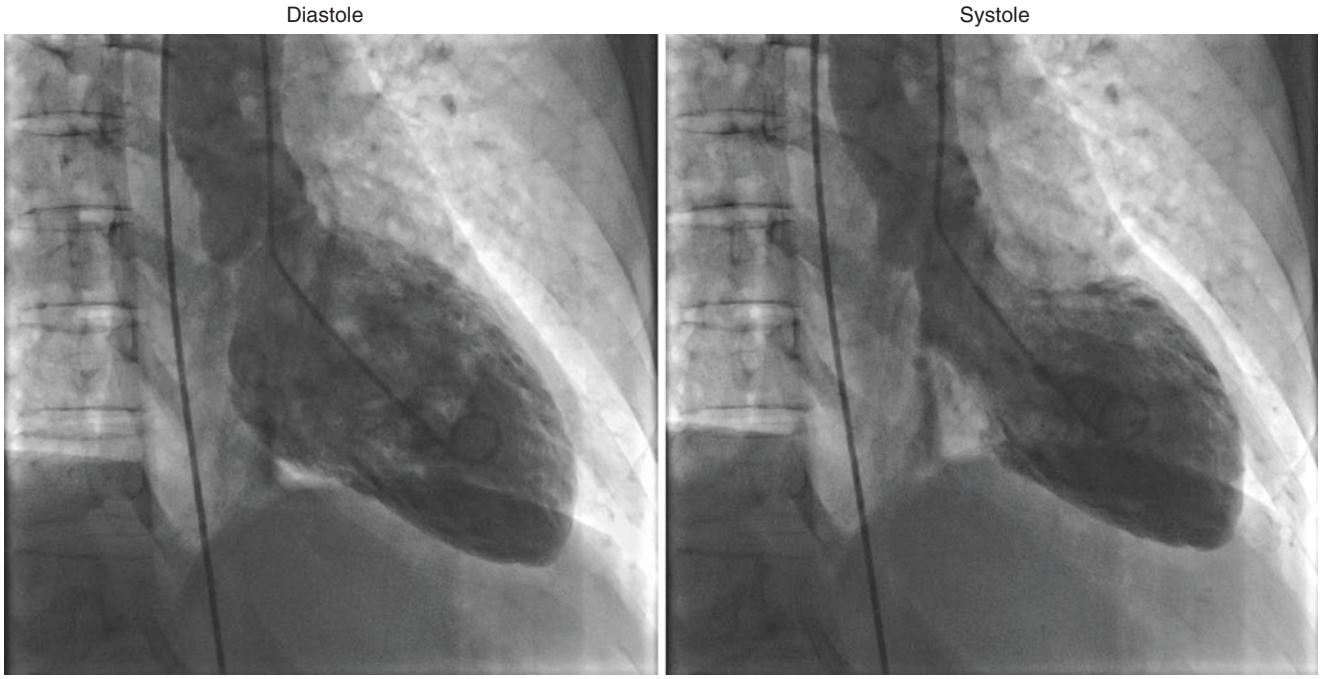


FIGURE 9-4

Apical ballooning in Takotsubo Cardiomyopathy in RAO projection

- Findings
  - Wall motion assessment
  - Ejection fraction
  - Presence of ventricular septal defect
  - Presence of left ventricular aneurysm or thrombus
    - True LV aneurysms have broad neck and are associated with akinetic wall. Pseudoaneurysms have narrow necks
  - Assessment of valvular regurgitation
    - **Sellar's criteria:** (1) partial filling of proximal chamber, (2) complete filling of proximal chamber but less dense than distal chamber, (3) equal opacification of proximal chamber in 4-5 beats, (4) equal opacification of proximal chamber in ≤3 beats

C) **Pressure assessment in left heart catheterization**

- AV gradient most accurately assessed by simultaneous aortic and LV pressures (e.g. double lumen pigtail catheter). Indicated when non-invasive results are inconclusive or discordant with clinical assessment (**Class I recommendation**). Not indicated when non-invasive results are conclusive (**Class III**).
- Mitral valve (MV) gradient assessed by simultaneous LV and pulmonary capillary wedge pressure (PCWP) or left atrial (LA) pressure

D) **Transseptal catheterization:**

- **Indications:** assessment of native or prosthetic mitral valve stenosis (PCWP overestimates transmitral gradient), percutaneous mitral valve commissurotomy or replacement, pulmonary vein isolation (electrophysiology), assessment of LVEDP in presence of mechanical AV
- **Complications:** tamponade, puncture of aortic root, atrial free wall, coronary sinus, or pulmonary artery (PA)

E) **Complications of left heart catheterization** [3]**:**

- Most common is access site related bleeding (<1% of diagnostic procedures versus 5–20% of PCIs, for femoral access); risk reduced further with transradial or ulnar access
- **Risk factors for access site complications:** age, female sex, smaller body surface area, obesity, emergent procedures, multi-vessel coronary artery disease (CAD), anti-platelet therapy, coagulopathy, renal dysfunction, liver dysfunction, pre-existing peripheral arterial disease and use of larger sheaths [4]
- **Vascular complications:** hematomas, compartment syndrome, retroperitoneal bleeding, pseudoaneurysm, atriovenous fistula, infection
- **Retroperitoneal bleed:** hypotension more so than back pain post procedure
  - Rapid recognition and management (massive transfusion and angiography) is critical for this life-threatening complication. Consider for **all post-procedural hypotension**; low threshold to transfuse early.
  - **CT scan** is recommended diagnostic modality if **clinically stable**
  - **Emergent peripheral angiography** is preferable for **unstable patients** given ability for concomitant intervention if indicated
- **Pseudoaneurysm:** pain, new bruit, or expansile pulse at access site, often day(s) after procedure
  - Treated with ultrasound-guided compression (small) or ultrasound-guided thrombin injection
- **Cerebrovascular Accident (0.07%):** MRI shows cerebral embolic events in 22% of patients after crossing severe aortic valve → majority are asymptomatic [5]
- **Other:** contrast induced nephropathy (CIN), myocardial infarction (0.05%), arrhythmia, perforation of cardiac chamber, coronary dissection and death

CONTRAST AGENTS

- **Nonionic low-osmolar contrast agents preferred**
  - Lower osmolality associated with lower risk of adverse reactions (arrhythmia, hypotension, nausea, increased LVEDP, pulmonary edema)
  - All agents have equal risk of contrast-induced nephropathy (CIN)
- **CIN** [6] **is defined as rise in creatinine >0.5 mg/dL or 25% above baseline within 48 h.**
  - Incidence: 2%
  - Increased risk in patient with chronic renal insufficiency, heart failure, diabetes mellitus (DM), anemia, significant intraprocedural contrast load and the elderly
  - Progression to end stage renal disease is very rare
  - Pre- and post-hydration reduces the risk of CIN
- Contrast allergy [7]
  - **Severe reactions (anaphylaxis) in ~1% of patients**
  - No association with shellfish allergy (common misconception)
  - **Prophylaxis:** 60 mg prednisone PO or 100 mg hydrocortisone IV at 12 h, 6 h and immediately prior to procedure, diphenhydramine 25–50 mg IV and ranitidine 150 mg PO within 1 h prior to contrast challenge

VASCULAR CLOSURE DEVICES

- **Four types:** suture, collagen plug, passive hemostatic patch, metallic clips
- Allows sheath removal in fully anti-coagulated patients and earlier ambulation (1–2 h versus 4–6 h)
- **No benefit and possible harm with regard to access site complications compared to manual compression** [8]**.**

RIGHT HEART CATHETERIZATION (RHC)

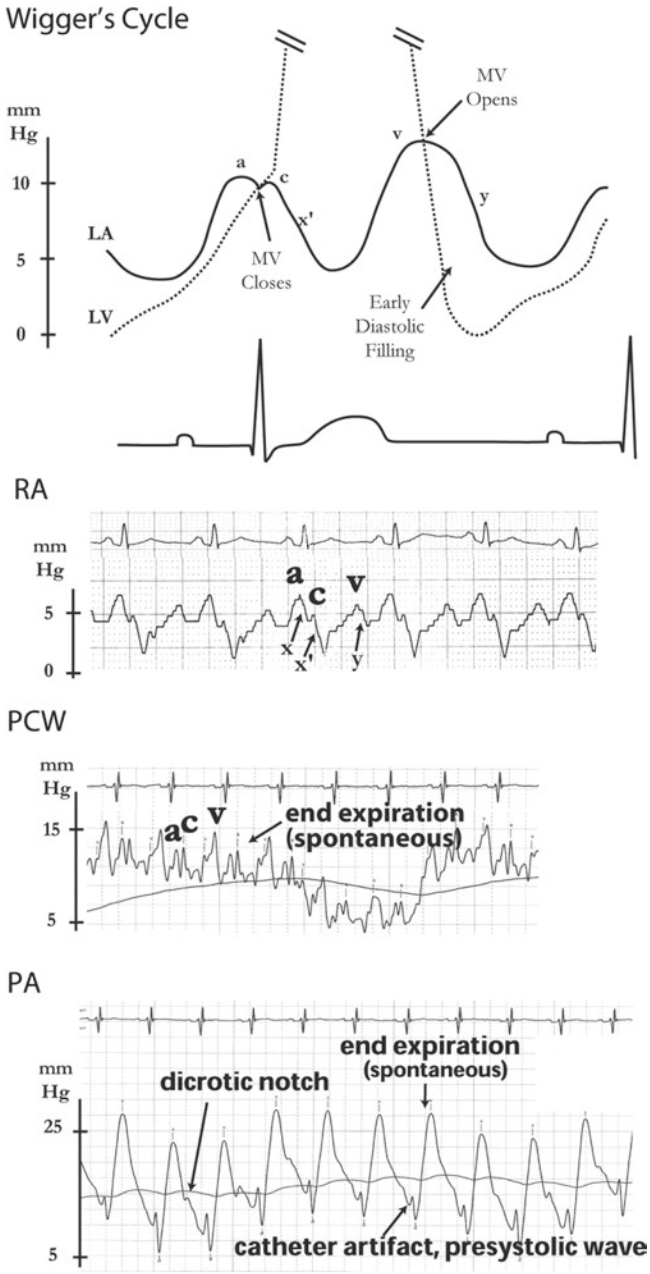
- **Indications for RHC:**
  - Cardiogenic shock
  - Discordant right and left heart failure
  - Complicated myocardial infarction (MI)
  - Severe chronic HF requiring supportive therapy
  - Diagnosis and assessment of pulmonary hypertension
  - Differentiation of septic vs. cardiogenic shock
  - Pericardial disease
  - Diagnosis and assessment of intracardiac shunts
  - Congenital heart disease
- **Complications**
  - Access site complication (e.g., carotid artery injury, pneumothorax, infection)
  - Arrhythmia
  - Right atrium (RA)/right ventricle (RV)/PA rupture
  - Pulmonary infarction
  - Complete heart block (esp. with baseline left bundle branch block)

A) **Pressure measurement** (Fig. 9-5, Table 9-1)**:**

- Zero reference pressure is established at the level of the atria
- **Atrial pressure:** three waves (orient using the ECG tracing):
  - **(a)** atrial systole (approx. correlates with QRS complex due to electro-mechanical delay)
  - **(c)** closing of AV valve
  - **(v)** RV systole (approx. correlates with T-wave)
- **Two descents:**
  - **(x)** atrial relaxation with open AV valve
  - **(x')** continued atrial relaxation with closed AV valve
  - **(y)** tricuspid valve opening
- **Spontaneous respirations:** pressure decreases with inspiration and increases with exhalation
  - This is reversed with mechanical respiration
  - Measure "peak" with "patient" breathing and "valley with "ventilator"
- PCWP gives good estimate of mean LA pressure but is delayed and blunted compared to direct LA pressure [9]
  - Equivalent to LAP and LVEDP in absence of MV disease

FIGURE 9-5

Right heart catheterization hemodynamics. *LA* left atrium, *LV* left ventricle, *MV* mitral valve, *PA* pulmonary artery, *PCWP* pulmonary capillary wedge pressure, *RA* right atrium



B) **Cardiac output (CO):**

- **Thermodilution**
  - Tends to underestimate CO with aortic regurgitation (AR), mitral regurgitation (MR) or tricuspid regurgitation (TR)
  - Inaccurate in low CO state (CO < 2.5 L/min), shunt or irregular rhythm
- **Fick Method**

$$CO_{Fick}\left(L/\min\right)=\frac{O_2\ \text{consumption}\left(mL/\min\right)}{\text{Arteriovenous}\,O_2\ \text{difference}\left(\text{vol}\%\right)\times 1.36\left(mL\,O_2/g\,Hgb\right)\times Hgb\left(mg/dL\right)\times 10}$$

TABLE 9-1

RHC NORMAL VALUES

MEASURE	NORMAL RANGE	COMMENT
Right atrium	1–6 (mmHg)	Equivalent to CVP and RVEDP in absence of TV disease
Right ventricle	15–25/1–8 (mmHg)	
Pulmonary artery	15–25/4–12 (mmHg)	
PCWP	4–12 (mmHg)	Equivalent to LAP and LVEDP in absence of MV disease
Left atrium	2–12 (mmHg)	
Left ventricle	90–140/5–12 (mmHg)	
Cardiac output	4–6 (L/min)	
Cardiac index	2.4–4 L/min/m^2	CO/BSA
Systemic vascular resistance (SVR)	700–1600 dynes×s/cm^5	SVR(Woods) = (MAP − RA)/CO 1 Wood = 80 dynes×s/cm^5
Pulmonary vascular resistance (PVR)	20–130 dynes×s/cm^5	PVR (Woods) = (Mean PA − PCWP)/CO > 240 dynes×s/cm^5 → limit heart transplant eligibility

BSA body surface area, *CO* cardiac output, *CVP* central venous pressure, *MAP* mean arterial pressure, *MV* mitral valve, *LAP* left atrial pressure, *LVEDP* left ventricular end diastolic pressure, *PA* pulmonary artery, *PCWP* pulmonary capillary wedge pressure, *RA* right atrium, *RVEDP* right ventricular end diastolic pressure, *TV* tricuspid valve

- – O_2 consumption (VO_2) ≈ 125 mL/min/m^2 (elevated in HF, fevers, sepsis, lung infections)
- – Largest source of error is oxygen consumption especially if assumed
- – **Not affected by TR or low output state**
- – Should not be used with severe MR or AI to calculate valve area since CO is not equivalent to transvalvular flow in the setting of severe regurgitation
- – Must be in steady state

■ **Angiographic Method:** tracing end diastolic and end systolic images

$$CO_{Angio} = \left(\text{end diastolic volume} - \text{end systolic volume}\right) \times \text{heart rate}$$

C) **Shunts:**

■ Screening for shunts by measuring oxygen saturation in superior vena cava (SVC) and PA

- – **Considered positive if difference >7%**
- – If positive, a full shunt run including SVC, vena cava (IVC), high-mid-low RA, RV inflow and outflow, main PA, right and left PA, pulmonary vein, LA, LV, and Aorta is performed

■ **Q_p:Q_s calculation**

$$\text{Pulmonary blood flow}\left(Q_p\right) = \frac{O_2 \text{ consumption}\left(\text{mL}/\text{min}/\text{m}^2\right)}{\text{Pulmonary venous } O_2 - \text{Pulmonary arterial } O_2}$$

$$\text{Systemic blood flow}\left(Q_s\right) = \frac{O_2 \text{ consumption}\left(\text{mL}/\text{min}/\text{m}^2\right)}{\text{Systemic arterial } O_2 - \text{Mixed venous } O_2}$$

$$\text{Shunt Fraction} = Q_p : Q_s = \frac{SAO_2 - MVO_2}{PVO_2 - PAO_2}$$

$$MVO_2 = \text{Saturation in the chamber proximal to the shunt} = \frac{3\left(SVCO_2\right)+\left(IVCO_2\right)}{4}$$

- SAO_2=Systemic arterial O_2, MVO_2=Mixed venous O_2, PVO_2=Pulmonary venous O_2 (systemic O_2 saturation can substitute for PVO_2), PAO_2=Pulmonary arterial O_2

D) **Calculation of Stenotic Valve Area (Gorlin Formula,** Fig. 9-6**):**

- Based on relationship between flow velocity, pressure gradient and area of stenotic valve
  - **AV area (AVA)** calculated based on flow during systole only (systolic ejection period (SEP))
  - **Mitral valve area (MVA)** is calculated based on flow during diastole (diastolic flow period (DFP)).

$$AVA\left(cm^2\right) = \frac{\text{Cardiac output}\left(L/\min\right)\times 1000\,mL/L}{44.3\times\text{Heart rate}\left(\text{beats}/\min\right)\times SEP\left(s\right)\times\sqrt{\text{mean gradient}\left(mmHg\right)}}$$

$$MVA\left(cm^2\right) = \frac{\text{Cardiac output}\left(L/\min\right)\times 1000\,mL/L}{37.7\times\text{Heart rate}\left(\text{beats}/\min\right)\times DEP\left(s\right)\times\sqrt{\text{mean gradient}\left(mmHg\right)}}$$

Simplified Hakki formula:

$$AVA\left(cm^2\right) = \frac{\text{Cardiac output}\left(L/\min\right)}{\sqrt{\text{mean gradient}\left(mmHg\right)}}$$

- **Limitations of the Gorlin formula:**
  - Errors in CO measurement are more important than errors in the pressure gradient measurement, because square root of the mean gradient is used in the formula
  - May underestimate the valve area in low CO states
  - May be inaccurate in mixed valvular disease (stenosis and regurgitation)
  - Does not apply to mechanical valves

CORONARY ANGIOGRAPHY

- **Gold standard** diagnostic test for diagnosing coronary artery disease and determining treatment options.

A) **Indications for coronary angiography are listed in** Table 9-2 [10–16]

- **Other Indications:**
  - Stable Coronary Artery Disease:
    - Patients with class I or II angina (only with strenuous or moderate exertion, respectively) despite medical therapy (**Class IIa**)
    - Patients with progression of stress test abnormalities (**Class IIa**)
    - Patients with high risk occupations and abnormal but not high-risk stress tests (**Class IIa**)
    - Revascularization of non-culprit lesions following STEMI with multi-vessel disease

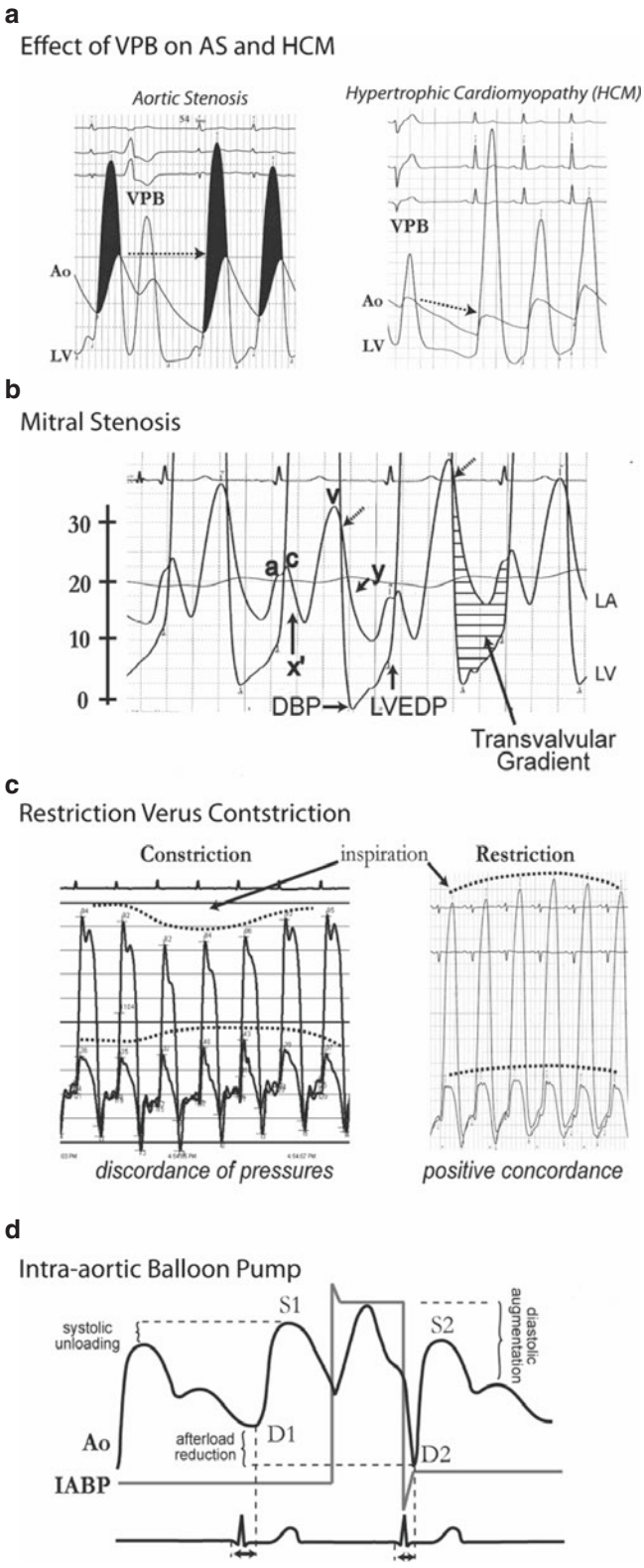


FIGURE 9-6

Common abnormal pressure tracings on right heart catheterization. *Ao* aorta, *AS* aortic stenosis, *DBP* diastolic blood pressure, *HCM* hypertrophic cardiomyopathy, *IABP* intraaortic baloon pump, *LA* left atrium, *LV* left ventricle, *LVEDP* left ventricular end diastolic pressure, *VPB* ventricular premature beat

TABLE 9-2

SUMMARY OF INDICATIONS FOR CORONARY ANGIOGRAPHY

	CLASS I	CLASS III
Nonspecific chest pain (CP)	High risk finding on noninvasive testing	No high-risk finding on non-invasive testing or repeat hospitalizations for chest pain
Stable coronary artery disease (CAD)	Survivors of sudden cardiac death (known or suspected CAD)	Patients with severe comorbidity where risks outweigh benefits
	Canadian Cardiovascular Society (CCS) class III and IV symptoms despite medications	CCS I or II with response to medical therapy and no evidence of ischemia on non-invasive testing
	High-risk criteria on non-invasive testing: LVEF < 35%; ST depressions >1 mm with low exercise capacity; hypotension with exercise; moderate to large area of ischemia (especially anterior wall).	Patient does not desire revascularization
	Heart failure symptoms and angina	
	Serious ventricular arrhythmia	
	Clinical characteristics indicate high likelihood of severe CAD	
Monitoring of symptoms in stable CAD	Marked limitation of ordinary activity despite maximal medical therapy	
ST-elevation MI	Candidates for primary PCI or rescue PCI	Patients not considered to be candidates for revascularization due to extensive comorbidities
	Cardiogenic shock and candidate for PCI	
	Prior to surgical repair of VSD or MR	
	Persistent hemodynamic or electric instability	
Post-STEMI hospitalization	Continued ischemia either spontaneous or with minimal exertion	Patients not considered to be candidates for revascularization
	Intermediate or high risk findings on non-invasive testing	
	Prior to definitive therapy for mechanical complications if sufficiently stable.	
	Persistent hemodynamic instability	
Unstable angina/NSTEMI (management)	Early invasive strategy in high risk patients: recurrent angina despite maximal medical therapy, positive biomarkers, HF symptoms (S3, pulmonary edema, MR), depressed LV function, hemodynamic or electrical instability, PCI in prior 6 months, prior CABG	Patients in whom risks of revascularization outweigh benefits
	High risk finding on non-invasive testing	Patients with chest pain but low probability of acute coronary syndrome (ACS)
UA/NSTEMI post discharge	Patients initially treated conservatively but with recurrent UA or CCS class III/IV angina despite medical therapy.	Repeat angiography not indicated in absence of change in symptoms or results of non-invasive testing
Printzmetal angina	Episodic chest pain with ST elevations that resolve with nitroglycerin or CCB	Provocative testing should not be done in patients with high-grade obstructive lesions
Cardiac syndrome X	If no ECGs are available from CP episodes, provocative testing to rule out coronary spasm	
Post-CABG	Low threshold for angiography if patients have recurrent symptoms of ischemia	Routine angiography is not indicated in asymptomatic patients post CABG
Post-PCI	Suspected stent thrombosis	Routine angiography is not indicated in asymptomatic patients post PCI

	Recurrent ischemia or high risk non-invasive testing within 9 months of PCI	
Prior to valvular surgery	Patients at risk of having CAD, reduced LV function, noninvasive testing consistent with ischemia	Not indicated in patients younger than 35 years old without risk factors for or symptoms suggestive of ischemia.
	Patient with mild to moderate valvular disease but with symptoms of ischemia (CCS > 1)	
Prior to non cardiac surgery	Angina not responsive to medical therapy	Known CAD but low risk non-invasive testing
	High risk finding on non-invasive testing	Asymptomatic patients post PCI or CABG
	Unstable angina/NSTEMI	Mild angina with preserved LV function and no high risk features on non-invasive tetsting
	Equivocal non-invasive testing in high risk patient undergoing high risk surgery	Patients older than 40 as part of evaluation for non-cardiac transplantation if non-invasive testing shows no high risk features.

CABG coronary artery bypass graft, *CCB* calcium channel blocker, *HF* heart failure, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *MR* mitral regurgitation, *NSTEMI* non-ST segment elevation MI, *PCI* percutaneous coronary intervention, *VSD* ventricular septal defect, *UA* unstable angina

- Periodic evaluation after heart transplantation (**Class IIb**)
- Prior to ascending aorta surgery or surgical correction of congenital or valvular heart disease
- Patients with hypertrophic cardiomyopathy with angina despite medical therapy
- Prior to cardiac transplantation (to assess donor heart)
- Heart failure or ventricular arrhythmias without explained cause

B) **Contraindications (none are absolute):**

- Severe anemia
- Severe electrolyte abnormalities
- Recent deterioration in renal function
- Uncontrolled severe hypertension
- Infection at planned access site
- Coagulopathy (INR > 1.8, generally not an issue with radial artery access)

C) **Angiographic Projections:**

- Use anatomic landmarks for orientation or right vs left and caudal vs cranial projection:
  - **Right anterior oblique:** ribs on right side of screen
  - **Left anterior oblique:** ribs tip on left side of screen
  - **Caudal:** Diaphragmatic silhouette towards bottom of the screen, best visualizes the left circumflex
  - **Cranial:** Diaphragmatic silhouette towards middle or top of the screen best visualizes the left anterior descending

D) **Normal Coronary Anatomy** (Fig. 9-7)**:**

- **LMCA** arises above the left aortic sinus and the right coronary artery (RCA) above the right aortic sinus.
  - Best viewed in antero-posterior (AP) projection
  - Ostium well seen in LAO cranial, mid-distal well seen in LAO caudal
- **LMCA** courses divides into left anterior descending (LAD) and left circumflex (LCx) (30% of population have a ramus intermedius branch)
  - Ramus courses similarly to diagonal or obtuse marginal artery
- **LAD** gives rise to 1–3 diagonal arteries (supplying anterior wall, anterolateral papillary muscle, and anterior RV wall) and septal arteries (supplying apical and anterior two-thirds of septum)
  - Best viewed with cranially angulated projections
  - Diagonal artery ostia best seen in LAO; define margin of heart in RAO projection
- **LCx** gives rise to 1–3 obtuse marginal arteries supplying the lateral wall.
  - Best viewed with caudally angulated projections
  - After third obtuse marginal branch, branches are termed posterolateral
- **RCA** gives rise to conus branch, marginal arteries (supply RV free wall), posterior descending artery (PDA) (supply posterior third of septum), and posterolateral branches (PLB) (supply inferior wall).
  - Sinoatrial artery arises from RCA in 60% of patients.
- **Dominance determined by the artery supplying the posterior wall**
  - 85% of patients are right dominant
  - In co-dominant circulation, PDA arises from RCA and PLV from LCx (Table 9-3)

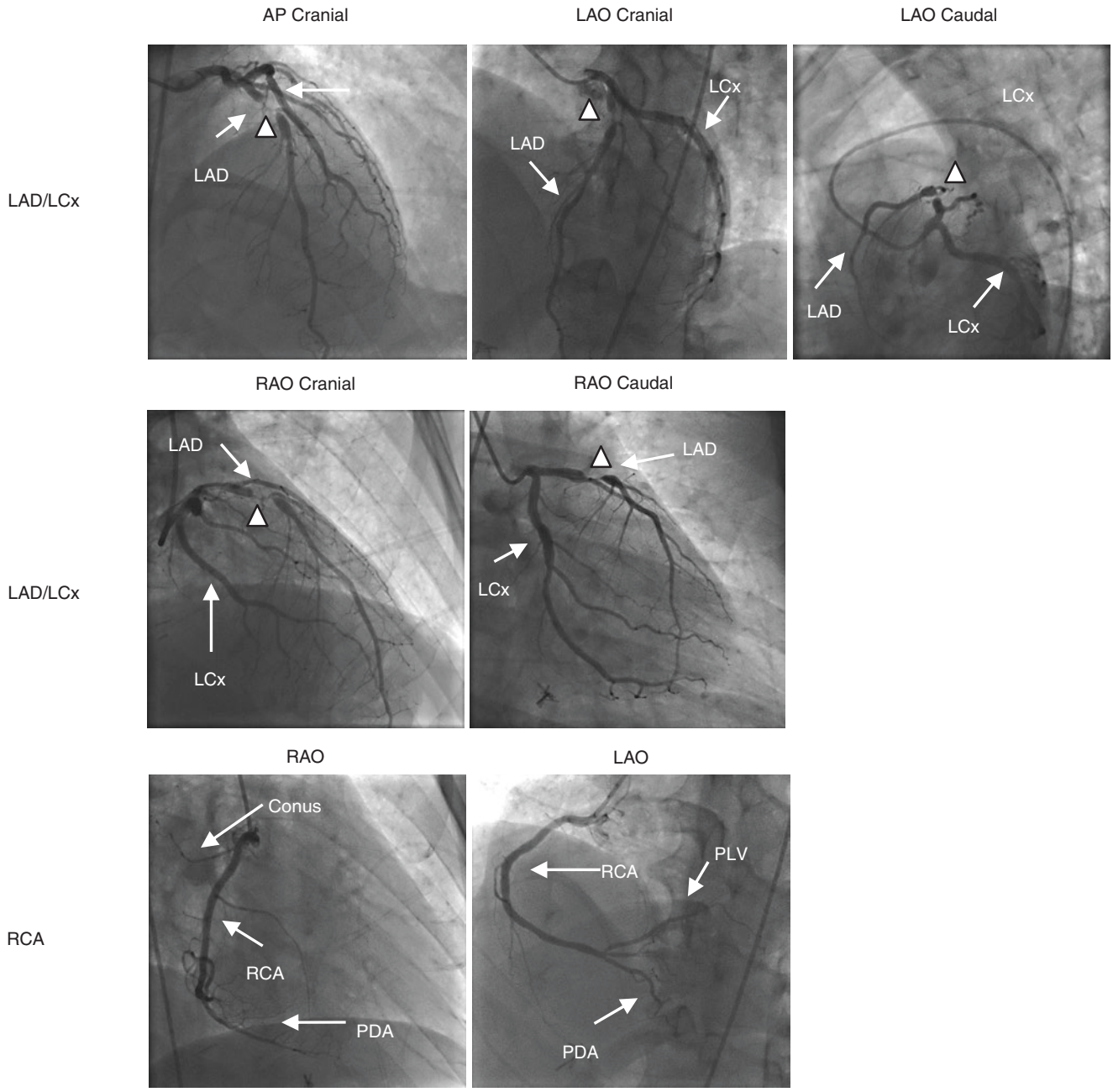


FIGURE 9-7

Standard angiographic projections in patient with 90% LAD lesion

E) **Special topics**

- **Dampening** of pressure wave form or ventricularization of waveform (decrease in diastolic pressure) due to occlusion of coronary artery with catheter, clot in catheter or catheter embedded in arterial well, selective engagement of conus artery when searching for RCA, coronary spasm.
  - Restore normal waveform prior to contrast injection to avoid risk of hydraulic trauma
- **Coronary spasm** secondary to catheter manipulation more common with RCA; may be treated with intracoronary nitroglycerin (Fig. 9-8)

TABLE 9-3

ANGIOGRAPHIC VIEWS

ARTERY	OSTIUM	COURSE OF VESSEL
LMCA	AP cranial, RAO caudal, LAO cranial, LAO caudal	AP cranial, LAO caudal
Proximal LAD	LAO cranial, RAO cranial, AP caudal	LAO cranial, LAO caudal, RAO cranial
Mid LAD	LAO cranial, RAO cranial	LAO cranial, LAO caudal, RAO cranial
Distal LAD	AP cranial, RAO cranial	LAO cranial, LAO caudal, RAO cranial
Diagonal	LAO cranial, RAO cranial	RAO cranial
Proximal LCx	RAO caudal, LAO caudal	LAO caudal
OM	RAO caudal, LAO caudal	RAO caudal
Proximal RCA	LAO	LAO, Right lateral
Mid RCA	RAO, LAO	LAO, Right lateral
Distal RCA	LAO cranial	LAO cranial
PDA	LAO cranial	RAO
PLV	RAO cranial	RAO cranial

AP anterior posterior, *LAD* left anterior descending, *LAO* left anterior oblique, *LCx* left circumflex, *LMCA* left main coronary artery, *PDA* posterior descending artery, *PLV* posterolateral vessel, *RAO* right anterior oblique, *RCA* right coronary artery

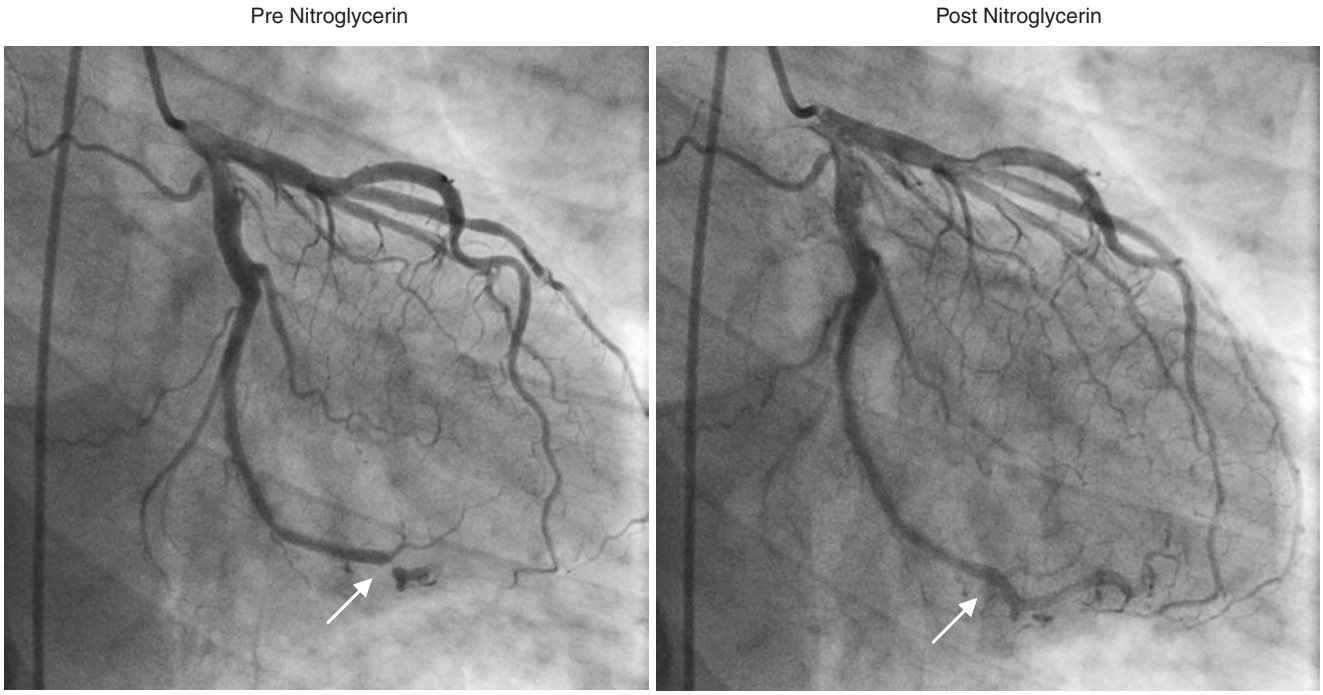


FIGURE 9-8

Coronary spasm

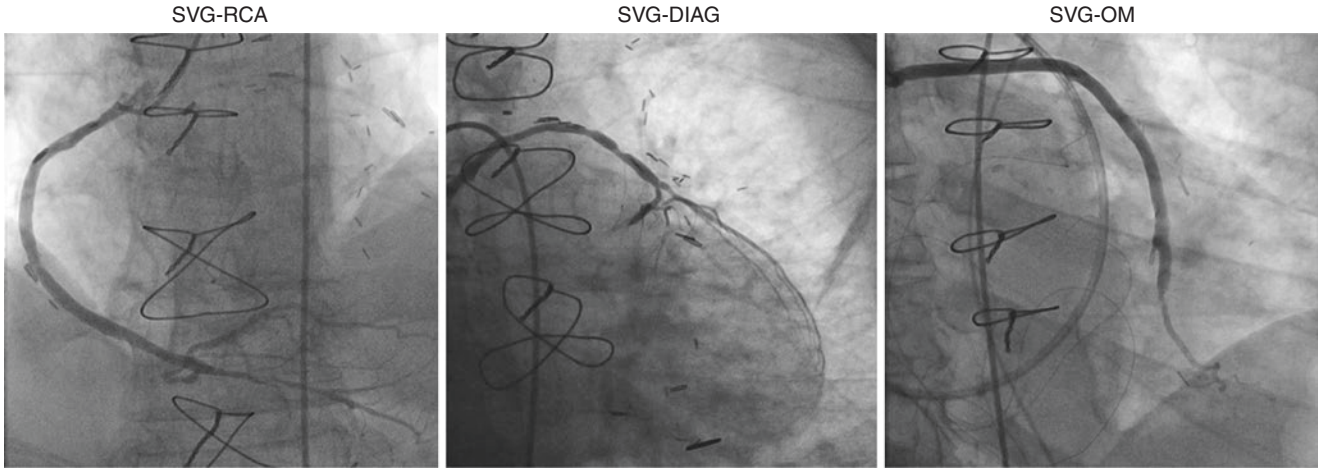


FIGURE 9-9

Saphenous vein grafts (SVG)

- Blood flow assessed by **TIMI criteria**:
  - **Grade 0:** no anterograde flow
  - **Grade 1:** contrast material passes lesion but does not opacify distal vessel
  - **Grade 2:** contrast opacifies distal vessel but the rate of flow distal to lesion is clearly slower than in non-obstructed arteries
  - **Grade 3**: flow distal to obstruction is equal to flow in non-obstructed arteries
- **Bypass grafts:** Important to obtain prior operative reports to guide search for grafts (Fig. 9-9)
  - Left radial arterial access or femoral arterial access preferred to engage LIMA graft.
  - **Saphenous vein grafts (SVG) to RCA** system typically arise in anterolateral aortic wall superior to native RCA.
  - **SVG to LAD or Diagonal artery** is usually above the RCA graft from the anterior aorta.
  - **SVG to LCx** system is typically superior to the SVG to LAD/diagonal artery and arise from anterolateral aorta.
  - **LIMA graft:** must rule out significant subclavian artery stenosis. Contralateral anterior oblique identifies IMA ostium. Left lateral view to assess the anastomosis of the LIMA to the LAD.

F) **Anomalous Coronary Arteries:**

- **Occur in up to 5% of population**
  - Majority are discovered incidentally and are of no clinical significance
  - **Most common anomaly is separate LAD and LCX ostia**; most lethal anomaly is left coronary with anomalous origin and intra-arterial course (Table 9-4)

G) **Collateral Circulation** (Fig. 9-10)**:**

- Develop in response to increased pressure gradient of pre-existing interarterial anastomoses
  - Can pressurize and be seen immediately following acute occlusion (e.g. STEMI)
  - Independent of subtended myocardium and **does not predict viability**

TABLE 9-4

CLASSIFICATION OF THE ANOMALOUS CORONARY ARTERY

Anomaly of origin and course
- Absence of left main trunk (Separate LAD and LCx ostia) - Anomalous location of coronary ostium, from pulmonary artery: must be corrected usually at birth. - Anomalous origination of coronary ostium from opposite coronary sinus, or non-cusped (posterior) sinus: course between aorta and RVOT associated with increased risk of SCD. Treat with CABG or PCI. - Single coronary artery - Myocardial bridging: maybe associated with ischemia. 5% of general population but 30–50% of patients with HCM. Treatment with medication versus PCI versus CABG not established.
Anomaly of intrinsic coronary artery anatomy
- Congenital ostial stenosis or atresia: often associated with other congenital disease. - Coronary ectasia or aneurysm: Kawasaki disease, connective tissue disease, arteritis → risk thrombosis and embolism. - Coronary hypoplasia - Intramural coronary artery (myocardial bridging): abrupt narrowing of vessel during systole. - Intercoronary communication
Anomaly of coronary termination
- Coronary artery fistula → terminate in RV (40%), RA (25%), PA (17%), coronary sinus or SVC. Asymptomatic in 50%. Associated with continuous murmur. Maybe cause ischemia, HF, arrhythmia. Treat with surgical closure or coil embolization

CABG coronary artery bypass graft, *HCM* hypertrophic cardiomyopathy, *HF* heart failure, *LAD* left anterior descending, *LCx* left circumflex, *PA* pulmonary artery, *PCI* percutaneous coronary intervention, *RA* right atrium, *RV* right ventricle, *RVOT* right ventricular outflow track, *SCD* sudden cardiac death, *SVC* superior vena cava

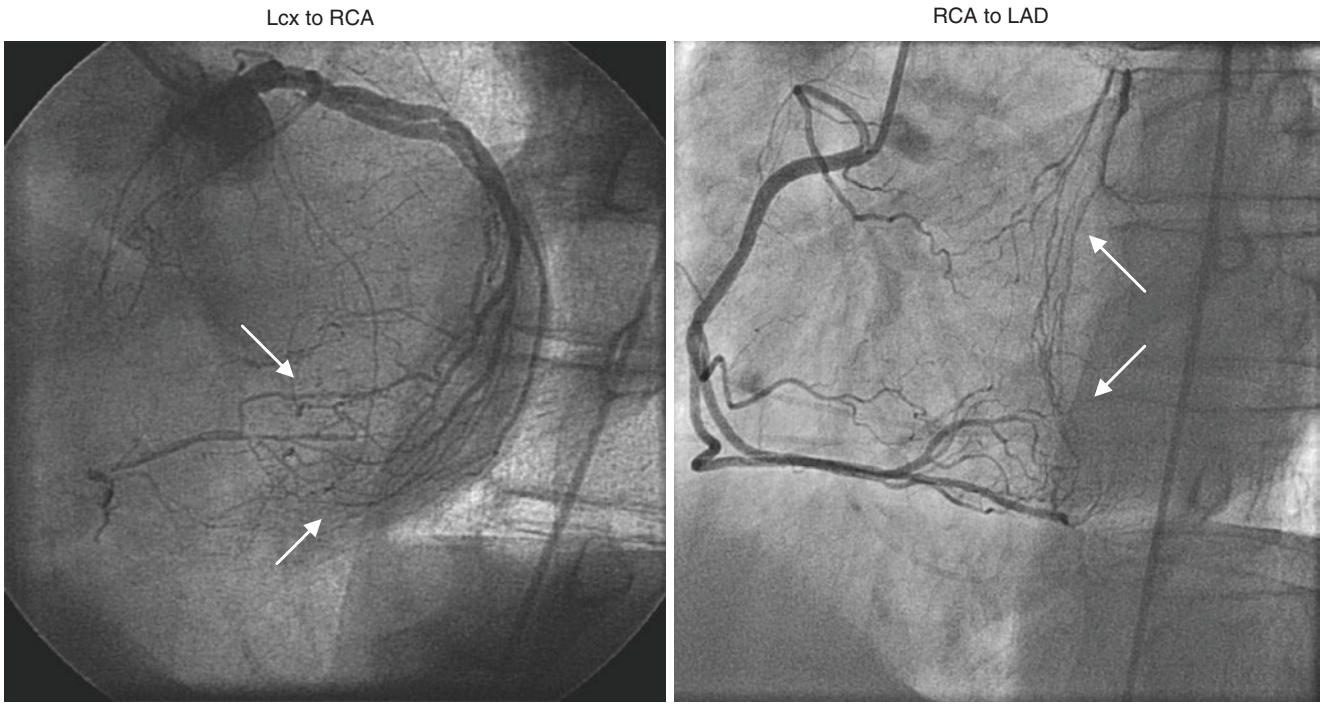


FIGURE 9-10

Collateral vessels visualized on angiogram

- Clear majority (90%) are inadequate to prevent ischemia during stress/FFR of a CTO territory [17]
- Rentrop classification
  - 0 = no filling
  - 1 = side branch filled
  - 2 = partial filling occluded artery
  - 3 = complete filling of occluded artery

H) **Assessing Coronary Lesions:**

- **Type A:** Discrete (<10 mm), concentric, non-angulated segment, smooth contour, minimal calcium, non-ostial, no thrombus, no significant side branch involvement.
- **Type B:** Tubular (<20 mm), eccentric, moderate angulation (45–90°), irregular, calcified, ostial, bifurcation, thrombus present, total occlusion <3 months.
- **Type C:** Diffuse (>20 mm), angulated >90°, bifurcation but unable to protect side branch, total occlusion >3 months (CTO), degenerated SVG.
- Flush occlusion or hazy stump and dye hang-up are consistent with thrombus (typically in patients presenting with acute coronary syndrome (ACS)) or dissection (consider iatrogenic or spontaneous coronary artery dissection, SCAD)

I) **Complications:**

- Stroke, air embolism, coronary artery thrombosis or dissection and vascular access site complications.
  - **Coronary artery dissection** usually secondary to uncontrolled or deep catheter engagement. If not significantly extended, can be treated with coronary stent.
  - **Stroke** risk is increased in patients with DM, renal failure, prior stroke, diseased ascending aorta, and during prolonged or urgent catheterizations.
  - **Air embolism:** prevention with meticulous technique is key. Treatment is generally limited to supportive therapy with 100% oxygen and hemodynamic support with inotropes and possible mechanical circulatory support such as IABP. May attempt injection of saline or adenosine into coronary artery to displace air.

J) **Limitations of Angiography:**

- Severity of angiographic stenosis for **intermediate lesions (40–70%) correlates poorly** with hemodynamic significance.
- Angiography alone cannot identify extent of plaque burden if plaque does not compromise luminal diameter.
- Overlapping coronary segments, tortuous vessels, and poor angiographic technique can result in inaccurate results.

INTRAVASCULAR DIAGNOSTICS

- Angiography provides a **limited 2-D silhouette of a complex 3-D structure** that correlates poorly with functional disease severity.

A) **Fractional Flow Reserve (FFR) and Instantaneous wave-Free Ratio (iFR):**

- **FFR** is the pressure gradient measured across the lesion or lesions in question under hyperemic conditions, typically with adenosine
  - Severity of gradient correlates with non-invasive assessment of ischemia and identifies provocable ischemia with **>90% accuracy**
  - Standard of care for functional assessment of intermediate severity lesions (40–80% angiographic stenosis)
  - **FFR recordings <0.80 correlate with ischemia and warrant revascularization** [18]
  - If the vessel in question collaterizes a chronic total occlusion (CTO), consider first revascularizing the CTO to avoid confounding the FFR assessment

- **Instantaneous wave-free pressure ratio (iFR)** has largely supplanted FFR
  - iFR uses the ratio of proximal and distal coronary pressures over the wave-free period in diastole.
  - Avoids adenosine use and may be used to screen moderate lesions [19]
  - **Values <0.89 have been demonstrated to be physiologically and clinically significant**
  - **"Hybrid approach"**
    - **Defer treatment if iFR >0.93**
    - **Treat if iFR <0.86**
    - **FFR if iFR ≥0.86 and ≤0.93**
  - Outcomes studies have demonstrated that iFR-guided revascularization strategy is non-inferior to FFR-guided strategy [20, 21]

B) **Intravascular Ultrasound (IVUS):**

- Provides cross-sectional image of vessel lumen and wall with **greater depth/penetration than OCT but less spatial resolution**
- **Indications:**
  - Assess lesion severity when unclear by angiography
    - Ostial LMCA disease (significant if minimum lumen area <6.0 mm^2) [22]
    - Bifurcation lesion
    - Borderline lesions (minimum lumen area <2.6 mm2 by IVUS in non-LMCA artery correlates with positive FFR) [23].
    - Measure plaque burden and characterize plaque content
  - Guide PCI
    - Determine stent size and extent of stent expansion.
    - Evaluate mechanism of stent failure in patients with in-stent thrombosis or restenosis.
  - Evaluation of transplant vasculopathy
  - Demonstrated benefit in left main and long-lesions
- Complications: coronary spasm (2%), dissection and perforation.

C) **Optical Coherence Tomography (OCT):** [24]

- Analogous to IVUS, OCT uses measures backscattered light ("optical echoes") to provide cross sectional vessel lumen and wall assessment with **greater spatial resolution than IVUS but less depth/penetration**.
- Significantly higher resolution (~10 μm) than IVUS (150 μm) but with less tissue penetration, allowing for detailed visualization of superficial coronary plaque morphology
- Experimental use to identify presence of vulnerable plaques with thin fibrous caps
  - Distinguish plaque rupture (need stent) versus coronary erosion (need only antiplatelet therapy)
- **Indications (similar to IVUS):** assess severity of lesion if unclear by angiography, guide PCI, evaluate etiology of post-PCI complications.
- Unlike IVUS, requires blood free vessel (typically flushed with contrast) during image acquisition.
- Benefit has not yet been demonstrated; under investigation currently

ENDOMYOCARDIAL BIOPSY

■ **Indications for endomyocardial biopsy:** [25]

- New onset heart failure (HF) <2 weeks with normal size or dilated LV and hemodynamic compromise (**Class I**)
- New onset HF 2 weeks to 3 months with dilated LV and ventricular arrhythmia or heart block or failure to respond to 1–2 weeks of medical therapy (**Class I**)
- Diagnosis of infiltrative cardiomyopathy (e.g. amyloid and sarcoid) (**Class IIa**)
- Monitoring of transplanted heart for rejection.

■ Complications of endomyocardial biopsy (**6% risk overall**):

- Cardiac perforation, very high mortality (0.5% risk)
- Ventricular arrhythmia (1% risk)
- Heart block (1% risk)
- Tricuspid injury (risk reduced with use of longer sheath)
- Venous access site complication (3%)

STRUCTURAL HEART INTERVENTION

A) **Transcatheter aortic valve replacement (TAVR)**

■ **Indications** [26, 27]

- TAVR or surgical aortic valve replacement (SAVR) for symptomatic aortic stenosis (stage D) with high surgical risk (**class I**)—STS risk >8%
- TAVR for symptomatic aortic stenosis (stage D) with prohibitive surgical risk and a predicted post-TAVR survival >12 months (**class I**)
- TAVR is a reasonable alternative to SAVR in severe symptomatic aortic stenosis (stage D) who have intermediate surgical risk (**class IIa**)—STS risk 3–8%
- Collaboration of Heart Team in the decision for transcatheter versus surgical approach (**class I**)
- **Contraindication to surgical aortic valve replacement include:**
  - Porcelain aorta
  - Mediastinal radiation
  - Pericardiectomy with adhesions
  - Sternal infection with reconstruction
  - LIMA graft underlying sternum
- Percutaneous aortic valvotomy may be used as a bridge to transcatheter or surgical valve replacement in severely symptomatic patients (**class IIb**)
- Failed surgical aortic valve replacements ("valve-in-valve") for bioprosthetic valve failure with stenosis or regurgitation
- Recent studies support at least equipoise of TAVR compared to SAVR (non-inferiority or even possible benefit) in low surgical risk patients—STS risk <3%
- TAVR for aortic insufficiency, and bicuspid anatomy are currently investigational in the US

B) **Left atrial appendage (LAA) closure** [28, 29]

■ Atrial fibrillation affects up to 6.1 million patients in the US and is responsible for up to one in five strokes in those >80 years of age
■ LAA is the most common source of cardioembolic stroke
■ LAA closure is now FDA approved as alternative for warfarin for stroke prevention in non-valvular atrial fibrillation

- Self-expanding nitinol cage deployed into LAA via transseptal puncture for stroke prevention

MECHANICAL CIRCULATORY SUPPORT

- **Indications** [30, 31]
  - Cardiogenic shock in patients with STEMI (**class Ib**)
  - Support during high risk PCI (e.g. EF < 35%, recent heart failure, unprotected left main coronary artery) (**class IIb**)
  - Other causes of cardiogenic shock (myocarditis, mechanical complications of myocardial infarction, e.g. ischemic mitral regurgitation, ventricular septal defect)
  - Refractory HF ("bridge-to-a-bridge" therapy)
  - Refractory angina
  - Refractory ventricular arrhythmia
- **Contraindications**
  - Aortic regurgitation
  - Aortic injury (aneurysm, dissection/hematoma)
  - Severe peripheral arterial disease
  - Left ventricular or atrial thrombus
  - Severe coagulopathy or sepsis
- **Intraaortic balloon counterpulsation (IABP)**
  - The most commonly used form of mechanical circulatory support
    - Hemodynamic effects (Fig. 9-5d)
      - Assisted systolic pressure (S2) < unassisted (S1)
      - Assisted diastolic pressure (D2) < unassisted (D1)
      - Augmented diastolic pressure > systolic pressure (S1 and S2)
      - Mean arterial pressure is increased. Afterload is reduced.
- **Left ventricle to aorta assist device**
  - Axial continuous flow catheter spans that aortic valve (inflow in the left ventricle and outflow into aorta) to offload the left ventricle and provide circulatory support
  - Up 5 L/min of cardiac output
- **Left atrium to aorta assist device**
  - Centrifugal continuous flow pump (inflow venous catheter in left atrium via transseptal puncture and arterial outflow catheter in the iliofemoral system)
  - Up 5 L/min of cardiac output

CHRONIC THROMBOTIC OCCLUSION (CTO) PCI

- CTO is present in up to one in three patients who undergo cardiac catheterization
- Revascularization of CTO is indicated for **medically refractory angina or asymptomatic patients with a large area of ischemia (IIa)** [31]
  - Primary barrier to successful CTO PCI is technical difficulty of antegrade approaches such as wire escalation strategies
    - Retrograde approach through septal or epicardial collateral channels using contemporary techniques by experienced operators may be required
    - Procedural mechanical circulatory support may be beneficial, particularly for severe left ventricular dysfunction or intervention of "last remaining vessel"
  - **Reasonable to pursue CTO PCI if:**
    - CTO is symptomatic or represents large area of myocardial ischemia
    - Downstream myocardium is viable

- Likelihood of success >60% with estimated risk of myocardial infarction or death ≤5%

– **Surgery preferred for CTO PCI:**

- Left main involvement
- Complex three-vessel disease, especially with diabetes, severe left ventricular dysfunction or chronic renal disease
- Proximal LAD supplies viable myocardium and anatomy is not favorable for PCI
- Multi-vessel CTO with low likelihood of complete revascularization

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Questions and Answers

1) A 51 year-old man presents with shortness of breath and dyspnea on exertion. TTE reveals a dilated RA and RV and a secundum ASD. He is taken for cardiac catheterization. Intracardiac pressures are RA 10, RV 66/6, PA 66/45, and PCW 10 mmHg. Cardiac output by thermodilution was 7.0 L/min. Oxygen saturations were IVC 68%, SVC 64%, RA 84%, RV 87%, PA 87%, Aorta 98%. What is the Qp/Qs?
   (a) 2.0: 1.0
   (b) 2.5: 1.0
   (c) 3.0: 1.0
   (d) Thermodilution is inaccurate in setting of shunt, therefore cannot calculate shunt fraction
   (e) Calculation of shunt fraction requires knowledge of oxygen consumption

   Answer: c

   - Qp/Qs is the ratio of pulmonary flow to systemic blood flow
   - Qp = Oxygen consumption/[PV O_2 content – PA O_2 content]
   - Qs = Oxygen consumption/[SA O_2 content – MV O_2 content]
   - O_2 content = 10 dL/L (1.34 mL/g × Hgb g/dL × O_2 saturation → ratio of Qp/Qs allows for cancelling out oxygen consumption and all components of oxygen content equation accept for O_2 saturation.
   - $MVO_2 = (3*SVC + IVC)/4 = 65\%$
   - $Qp/Qs = [SAO_2 - MVO_2]/[PVO_2 - PAO_2] \rightarrow (98\% - 65\%)/(98 - 87) = 31/11 \rightarrow 3.0: 1$

2) A 77 year-old man with severe aortic stenosis and regurgitation is taken for cardiac catheterization. Left heart catheterization reveals a mean gradient of 49 mmHg. Cardiac output by thermodilution is calculated to be 4.9 L/min and by the Fick method is calculated to be 5.1 L/min. The aortic valve area measured by Doppler (continuity equation) is 2.0 cm^2. Which of the following statements is most accurate?
   (a) Doppler measurement of AVA using the continuity equation overestimates AVA in the context of severe aortic regurgitation.
   (b) The true aortic valve area is greater than the valve area calculated by cardiac catheterization in patients with aortic regurgitation.
   (c) In the context of severe aortic regurgitation, thermodiluation is more accurate than the Fick method in determining cardiac output.
   (d) Aortic regurgitation does not affect the calculated AVA using the Gorlin formula

   Answer: b

   Calculation of aortic valve area both by Doppler and by the Gorlin formula depends on accurate measurement of blood flow across the valve. In the context of severe aortic regurgitation, cardiac output measured by thermodilation and the Fick method underestimate blood flow across the aortic valve. As result, the calculated AVA is an underestimation. Assuming relatively normal cardiac output, both the thermodilation and Fick methods can give accurate measurements of cardiac output in the setting of severe aortic stenosis.

3) A 79 year-old man complaints of chest pain and shortness of breath with exertion and moderate to severe aortic stenosis by TTE is taken for cardiac catheterization. The study reveals:

   - RA: 8 mmHg
   - PA: 45/20 mmHg
   - PCWP: 16 mmHg
   - Cardiac output by thermodilution: 4.0 L/min
   - LV: 190/15 mmHg
   - Aorta: 132/60 mmHg
   - Mean aortic gradient: 55 mmHg
   - Heart rate: 70 beats per minute
   - SEP: 320 ms
   - Coronary arteries reveal a 60% mid LAD lesion with no significant CAD elsewhere.

   Based on the information above, what is the calculated AVA?
   (a) 0.5 cm^2
   (b) 0.75 cm^2
   (c) 1.0 cm^2
   (d) 1.5 cm^2
   (e) There is not enough information to calculate the AVA

   Answer: b

   The Gorlin formula is used to calculate AVA.

$$AVA = [CO \times 1000] \,/\, \begin{bmatrix} 44.3 \times HR(\text{bpm}) \times SEP(\text{s/beat}) \\ \times \sqrt{\text{mean AV gradient}} \end{bmatrix}$$

$$AVA = [4.0 \times 1000] \,/\, [44.3 \times 70 \times 0.23 \times \sqrt{55}] = 0.75 \text{ cm}^2$$

4) A 56 year-old woman presents with chest pain that occurs randomly both at rest and with exertion. The pain is sub-sternal pressure like but does not radiate. She is taken for an adenosine MIBI stress test which reveals mild apical ischemia. Based on these findings she is taken for cardiac catheterization. Coronary angiography reveals a 60% mid-LAD lesion and no other significant epicardial disease. Which of the following is the most accurate method to determine if the LAD lesion is clinically significant?
   (a) No further study is needed because of the correlation of angiography with stress test results.
   (b) Fractional flow reserve
   (c) OCT assessment of minimal luminal area in the LAD stenosis
   (d) IVUS assessment of plaque area at the site of stenosis

   Answer: b

   Fractional flow reserve is the most accurate method of determining the hemodynamic significance of intermediate severity lesions. Mild apical ischemia on stress tests in woman is often caused by breast artifact. While OCT and IVUS can both give accurate measurements of luminal area, the correlation of luminal area with hemodynamic significance is limited.

5) The following statements regarding vascular access and diagnostic coronary angiography are true, except:
   (a) Transradial artery access generally offers reduced risk of major bleeding, death, and major adverse cardiovascular events compared to transfemoral artery access
   (b) Coronary angiography is indicated for all patients with infective endocarditis undergoing cardiac surgery
   (c) Coronary angiography is a safe diagnostic procedure with risk of major bleeding complication is <1% and risk of death, myocardial infarction, or stroke is approximately <0.1%
   (d) One French unit (Fr) is equivalent to 1/3-mm

   Answer: b

   Diagnostic coronary angiography is a relative safe procedure with the biggest risk related to vascular access. Risk of catastrophic complication of death, myocardial infarction, or stroke is approximately <0.1%. These risks, particularly related to bleeding and also notably mortality, are reduced with the transradial approach. Diagnostic coronary angriography before cardiac surgery for infective endocarditis is indicated for evidence of coronary emolization (Class I) but not for patients without cardiac risk factors or evidence of coronary embolization (Class III). Angiography may be considered for those patients with history of coronary disease, multiple risk factors or advanced age (Class IIb).

6) A 69-year-old man with history of coronary artery disease underwent non-cardiac surgery and was noted to have chest pressure for several hours that resolved without specific intervention. The cardiology service is consulted the following day and review of his ECG reveals ST elevation at the time of chest pain that was not recognized. The patient is now free of chest pain, has evolved inferior q-waves, and 20-h have passed since onset of symptoms. What is the next best step in the patient's management?
   (a) Urgent thrombolytic therapy
   (b) Urgent cardiac catheterization with intent for purcutaneous revascularization
   (c) Initiate glycoprotein IIb/IIIa inhibitor therapy
   (d) Medically manage the patient for likely completed myocardial infarction

   Answer: d

   The patient is over 12 h from onset of symptoms and has no evidence of ongoing myocardial ischemia (he is chest pain free and the ECG no longer shows acute infarction), suggesting that he suffered a complete myocardial infarction. At this point, urgent coronary angiography or thrombolytic therapy are (class III). Early coronary angiography with intent for purcutaneous revascularization is indicated only within 12 h of symptom onset (Class I).

7) A 54-year-old man hypertension presents to the Emergency Department with severe chest pain at rest. The ECG is normal and cardiac biomarkers are negative. This is his second presentation for similiar symptoms within the past year despite optimal medical therapy. His prior cardiac evaluation includes a Bruce protocol streadmill stress test 5 years ago and coronary angiography with provocative testing performed 4 years ago which were normal. What is the next best step in the patient's management?
   (a) Repeat coronary angiography
   (b) Repeat Bruce protocol treadmill stress test
   (c) Exercise stress test with myocardial perfusion imaging
   (d) Coronary-gated CT angiogram

   Answer: c

   This patient presents with recurrent chest discomfort suggestive of unstable angina but without objective evidence of ischemia. Repeat coronary angiogram is contraindicated (class III) given the normal study within the past 5 years. Repeat ECG-based stress testing and cardiac CT angiography are unlikely to provide any additional information. Additional stress testing with myocardial perfusion imaging, hoewver, may provide evidence of dysfunctional microvascular disease. Up to 15% of patients who present with unstable angina are found to have no significant epicardial coronary disease and one-third of these patients may have impaired microvascular coronary disease. Prognosis is good and management is centered on reassurance and continuation of optimal medical therapy.

8) A 39-year-old woman who is 36-weeks pregnant presents with severe chest pain at rest for the past hour. ECG reveals anterior ST elevation. What is the next best step in the patient's management?
   (a) Urgent cardiac catheterization and percutaneous coronary intervention
   (b) Immediate transthoracic echocardiography for wall motion abnormalities
   (c) Medical management
   (d) Contrast-enhanced chest CT

   Answer: a

This patient presents with acute anterior myocardial infarction (MI) in the context of pregnancy. Though MI is rare in woman of child-bearing age, pregnancy increases the risk of MI by three- to fourfold. The etiology of MI during pregnancy is generally atherosclerotic, although spontaneous coronary artery dissection must be considered. If appropriate, percutaneous coronary intervention must be pursued without delay just as in the management of MI outside the peripartum period. Echocardiography and chest CT would unnecessarily delay diagnostic coronary angiography which is not contraindicated in pregnancy.

APPENDIX: ACC/AHA CONSENSUS GUIDELINES FOR CORONARY ANGIOGRAPHY

RECOMMENDATIONS FOR CORONARY ANGIOGRAPHY IN PATIENTS WITH KNOWN OR SUSPECTED CAD WHO ARE CURRENTLY ASYMPTOMATIC OR HAVE STABLE ANGINA

CLASS	RECOMMENDATION	LOE
I	CCS class III and IV angina on medical treatment	B
	High-risk criteria on noninvasive testing regardless of anginal severity	A
	Patients who have been successfully resuscitated from sudden cardiac death or have sustained (>30 s) monomorphic ventricular tachycardia or nonsustained (<30 s) polymorphic ventricular tachycardia.	B
IIa	CCS class III or IV angina, which improves to class I or II with medical therapy	C
	Serial noninvasive testing with identical testing protocols, at the same level of medical therapy, showing progressively worsening abnormalities	
	Patients with angina and suspected coronary disease who, due to disability, illness, or physical challenge, cannot be adequately risk stratified by other means	C
	CCS class I or II angina with intolerance to adequate medical therapy or with failure to respond, or patients who have recurrence of symptoms during adequate medical therapy as defined above	C
	Individuals whose occupation involves the safety of others (e.g., pilots, bus drivers, etc) who have abnormal but not high-risk stress test results or multiple clinical features that suggest high risk.	C
IIb	CCS class I or II angina with demonstrable ischemia but no high-risk criteria on noninvasive testing	C
	Asymptomatic man or postmenopausal woman without known coronary heart disease with >2 major clinical risk factors and abnormal but not high-risk criteria on noninvasive testing (performed for indications stated in the ACC/AHA noninvasive testing guidelines)	C
	Asymptomatic patients with prior MI with normal resting left ventricular function and ischemia on noninvasive testing but without high-risk criteria	C
	Periodic evaluation after cardiac transplantation	C
	Candidate for liver, lung, or renal transplant >40 years old as part of evaluation for transplantation	C
III	Angina in patients who prefer to avoid revascularization even though it might be appropriate	C
	Angina in patients who are not candidates for coronary revascularization or in whom revascularization is not likely to improve quality or duration of life	C
	As a screening test for CAD in asymptomatic patients	C
	After coronary artery bypass grafting (CABG) or angioplasty when there is no evidence of ischemia on noninvasive testing, unless there is informed consent for research purposes	C
	Coronary calcification on fluoroscopy, electron beam computed tomography, or other screening tests without criteria listed above	C

RECOMMENDATIONS FOR CORONARY ANGIOGRAPHY IN PATIENTS WITH NONSPECIFIC CHEST PAIN

CLASS	RECOMMENDATION	LOE
I	High-risk findings on noninvasive testing	B
IIb	Patients with recurrent hospitalizations for chest pain who have abnormal (but not high-risk) or equivocal findings on noninvasive testing	B
III	All other patients with nonspecific chest pain	C

RECOMMENDATIONS FOR CORONARY ANGIOGRAPHY IN UNSTABLE CORONARY SYNDROMES

CLASS	RECOMMENDATION	LOE
I	High or intermediate risk for adverse outcome in patients with unstable angina refractory to initial adequate medical therapy, or recurrent symptoms after initial stabilization. Emergent catheterization is recommended	B
	High risk for adverse outcome in patients with unstable angina. Urgent catheterization is recommended.	B
	High- or intermediate-risk unstable angina that stabilizes after initial treatment	A
	Initially low short-term–risk unstable angina that is subsequently high risk on noninvasive testing	B
	Suspected Prinzmetal variant angina	C
IIb	Low short-term–risk unstable angina, without high-risk criteria on noninvasive testing	C
III	Recurrent chest discomfort suggestive of unstable angina but without objective signs of ischemia and with a normal coronary angiogram during the past 5 years	C
	Unstable angina in patients who are not candidates for coronary revascularization or in patients for whom coronary revascularization will not improve the quality or duration of life	C

RECOMMENDATIONS FOR CORONARY ANGIOGRAPHY IN PATIENTS WITH POSTREVASCULARIZATION ISCHEMIA

CLASS	RECOMMENDATION	LOE
I	Suspected abrupt closure or subacute stent thrombosis after percutaneous revascularization	B
	Recurrent angina or high-risk criteria on noninvasive evaluation within 9 months of percutaneous revascularization	C
IIa	Recurrent symptomatic ischemia within 12 months of coronary artery bypass graft	B
	Noninvasive evidence of high-risk criteria at any time postoperatively	B
	Recurrent angina inadequately controlled by medical means after revascularization	C
IIb	Asymptomatic post-PTCA patient suspected of having restenosis within the first months after angioplasty because of an abnormal noninvasive test result but without noninvasive high-risk criteria	B
	Recurrent angina without high-risk criteria on noninvasive testing occurring >1 year postoperatively	C
	Asymptomatic postbypass patient in whom a deterioration in serial noninvasive testing has been documented but who is not at high risk on noninvasive testing	C
III	Symptoms in a postbypass patient who is not a candidate for repeat revascularization	C
	Routine angiography in asymptomatic patients after percutaneous transluminal coronary angioplasty (PTCA) or other surgery, unless as part of an approved research protocol	C

RECOMMENDATIONS FOR CORONARY ANGIOGRAPHY DURING THE INITIAL MANAGEMENT OF ACUTE MI (MI SUSPECTED AND ST ELEVATION OR BBB PRESENT WITH THE INTENT TO PERFORM PRIMARY PTCA)

CLASS	RECOMMENDATION	LOE
I	As an alternative to thrombolytic therapy in patients who can undergo angioplasty of the infarct artery within 12 h of the onset of symptoms or beyond 12 h if ischemic symptoms persist, *if performed in a timely fashion*[a] *by individuals skilled in the procedure*[b] *and supported by experienced personnel in an appropriate laboratory environment.*[c]	A
	In patients who are within 36 h of an acute ST elevation/Q-wave or new LBBB MI who develop cardiogenic shock, are <75 years of age, and in whom revascularization can be performed within 18 h of the onset of shock.	
IIa	As a reperfusion strategy in patients who are candidates for reperfusion but who have a contraindication to fibrinolytic therapy, if angioplasty can be performed as outlined above in class I.	C
III	In patients who are beyond 12 h from onset of symptoms and who have no evidence of myocardial ischemia	A
	In patients who are eligible for thrombolytic therapy and are undergoing primary angioplasty by an unskilled operator in a laboratory that does not have surgical capability	B

[a]Performance standard: within 90 min
[b]Individuals who perform >75 PTCA procedures per year
[c]Centers that perform >200 PTCA procedures per year and have cardiac surgical capability

RECOMMENDATIONS FOR EARLY CORONARY ANGIOGRAPHY IN THE PATIENT WITH SUSPECTED MI (ST-SEGMENT ELEVATION OR BBB PRESENT) WHO HAS NOT UNDERGONE PRIMARY PTCA

CLASS	RECOMMENDATION	LOE
IIa	Cardiogenic shock or persistent hemodynamic instability	B
IIb	Evolving large or anterior infarction after thrombolytic treatment when it is believed that reperfusion has not occurred and rescue PTCA is planned	B
	Marginal hemodynamic status but not actual cardiogenic shock when standard management (optimizing filling pressures) does not result in improvement	C
III	In patients who have received thrombolytic therapy and have no symptoms of ischemia	A
	Routine use of angiography and subsequent PTCA within 24 h of administration of thrombolytic agents	A

RECOMMENDATIONS FOR EARLY CORONARY ANGIOGRAPHY IN ACUTE MI (MI SUSPECTED BUT NO ST-SEGMENT ELEVATION)

CLASS	RECOMMENDATION	LOE
I	Persistent or recurrent (stuttering) episodes of symptomatic ischemia, spontaneous or induced, with or without associated ECG changes	A
	The presence of shock, severe pulmonary congestion, or continuing hypotension	B

RECOMMENDATIONS FOR CORONARY ANGIOGRAPHY DURING THE HOSPITAL-MANAGEMENT PHASE (PATIENTS WITH Q-WAVE AND NON–Q-WAVE INFARCTION)

CLASS	RECOMMENDATION	LOE
I	Spontaneous myocardial ischemia or myocardial ischemia provoked by minimal exertion, during recovery from infarction	A
	Before definitive therapy of a mechanical complication of infarction such as acute mitral regurgitation, ventricular septal defect, pseudoaneurysm, or left ventricular aneurysm	C
	Persistent hemodynamic instability	B
IIa	When MI is suspected to have occurred by a mechanism other than thrombotic occlusion at an atherosclerotic plaque (e.g., coronary embolism, arteritis, trauma, certain metabolic or hematologic diseases, or coronary spasm)	C
	Survivors of acute MI with LVEF < 0.40, CHF, prior revascularization, or malignant ventricular arrhythmias	C
	Clinical heart failure during the acute episode, but subsequent demonstration of preserved left ventricular function (LVEF > 0.40)	C
IIb	Coronary angiography to find a persistently occluded infarct-related artery in an attempt to revascularize that artery (open artery hypothesis)	C
	Coronary angiography performed without other risk stratification to identify the presence of left main or three-vessel disease	C
	All patients after a non-Q-wave MI	C
	Recurrent ventricular tachycardia and/or ventricular fibrillation, despite antiarrhythmic therapy, without evidence of ongoing myocardial ischemia	C
III	Patients who are not candidates for or who refuse coronary revascularization	C

RECOMMENDATIONS FOR CORONARY ANGIOGRAPHY DURING THE RISK-STRATIFICATION PHASE (PATIENTS WITH ALL TYPES OF MI)

CLASS	RECOMMENDATION	LOE
I	Ischemia at low levels of exercise with ECG changes (>1-mm ST-segment depression or other predictors of adverse outcome) and/or imaging abnormalities	B
IIa	Clinically significant CHF during the hospital course	C
	Inability to perform an exercise test with LVEF < 0.45	C
IIb	Ischemia occurring at high levels of exercise	C
	Non-Q-wave MI in a patient who is an appropriate candidate for a revascularization procedure	C
	Need to return to an unusually active form of employment	C
	Remote history of MI without evidence of CHF during the current event and without evidence of inducible ischemia	C
	Recurrent ventricular tachycardia, fibrillation, or both, despite antiarrhythmic therapy, without ongoing myocardial ischemia	C
III	Patients who are not candidates for or who refuse coronary revascularization	C

RECOMMENDATIONS FOR CORONARY ANGIOGRAPHY IN PERIOPERATIVE EVALUATION BEFORE (OR AFTER) NONCARDIAC SURGERY

CLASS	RECOMMENDATION	LOE
I	Evidence for high risk of adverse outcome based on noninvasive test results	C
	Angina unresponsive to adequate medical therapy	C
	Unstable angina, particularly when facing intermediate[a] or high-risk[a] noncardiac surgery	C
	Equivocal noninvasive test result in a high-clinical risk[b] patient undergoing high-risk[a] surgery	C
IIa	1. Multiple intermediate-clinical-risk markers[b] and planned vascular surgery	B
	Ischemia on noninvasive testing but without high-risk criteria	B
	Equivocal noninvasive test result in intermediate clinical-risk[b] patient undergoing high-risk[a] noncardiac surgery	C

CLASS	RECOMMENDATION	LOE
	Urgent noncardiac surgery while convalescing from acute MI	C
IIb	Perioperative MI	B
	Medically stabilized class III or IV angina and planned low-risk or minor[a] surgery	C
III	Low-risk[a] noncardiac surgery, with known CAD and no high-risk results on noninvasive testing	B
	Asymptomatic after coronary revascularization with excellent exercise capacity (>7 METs)	C
	Mild stable angina with good left ventricular function and no high-risk noninvasive test results	B
	Noncandidate for coronary revascularization owing to concomitant medical illness, severe left ventricular dysfunction (e.g., LVEF < 0.20), or refusal to consider revascularization	C
	Candidate for liver, lung, or renal transplant >40 years old as part of evaluation for transplantation, unless noninvasive testing reveals high risk for adverse outcome	C

[a]Cardiac risk according to type of noncardiac surgery. High risk: emergent major operations, aortic and major vascular, peripheral vascular, anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss; intermediate risk: carotid endarterectomy, major head and neck, intraperitoneal and/or intrathoracic, orthopedic surgery, prostate surgery; low risk: endoscopic procedures, superficial procedures, cataract surgery, breast surgery

[b]Cardiac risk according to clinical predictors of perioperative death, MI, or CHF. High clinical risk: unstable angina, recent MI and evidence of important residual ischemic risk, decompensated CHF, high degree of atrioventricular block, symptomatic ventricular arrhythmias with known structural heart disease, severe symptomatic valvular heart disease, multiple intermediate risk markers such as prior MI, CHF, and diabetes; intermediate clinical risk: CCS class I or II angina, prior MI by history or ECG, compensated or prior CHF, diabetes mellitus

RECOMMENDATIONS FOR USE OF CORONARY ANGIOGRAPHY IN PATIENTS WITH VALVULAR HEART DISEASE

CLASS	RECOMMENDATION	LOE
I	Before valve surgery or balloon valvotomy in an adult with chest discomfort, ischemia by noninvasive imaging, or both	B
	Before valve surgery in an adult free of chest pain but of substantial age and/or with multiple risk factors for coronary disease	C
	Infective endocarditis with evidence of coronary embolization	C
IIb	During left-heart catheterization performed for hemodynamic evaluation before aortic or mitral valve surgery in patients without preexisting evidence of coronary disease, multiple CAD risk factors, or advanced age.	C
III	Before cardiac surgery for infective endocarditis when there are no risk factors for coronary disease and no evidence of coronary embolization	C
	In asymptomatic patients when cardiac surgery is not being considered	C
	Before cardiac surgery when preoperative hemodynamic assessment by catheterization is unnecessary, and there is neither preexisting evidence of coronary disease nor risk factors for CAD.	C

RECOMMENDATIONS FOR USE OF CORONARY ANGIOGRAPHY IN PATIENTS WITH CONGENITAL HEART DISEASE

CLASS	RECOMMENDATION	LOE
I	Before surgical correction of congenital heart disease when chest discomfort or noninvasive evidence is suggestive of associated CAD	C
	Before surgical correction of suspected congenital coronary anomalies such as congenital coronary artery stenosis, coronary arteriovenous fistula, and anomalous origin of left coronary artery	C
	Forms of congenital heart disease frequently associated with coronary artery anomalies that may complicate surgical management.	C
	Unexplained cardiac arrest in a young patient	B
IIa	Before corrective open heart surgery for congenital heart disease in an adult whose risk profile increases the likelihood of coexisting coronary disease	C
IIb	During left-heart catheterization for hemodynamic assessment of congenital heart disease in an adult in whom the risk of coronary disease is not high	C
III	In the routine evaluation of congenital heart disease in asymptomatic patients for whom heart surgery is not planned	C

RECOMMENDATIONS FOR USE OF CORONARY ANGIOGRAPHY IN PATIENTS WITH CHF

CLASS	RECOMMENDATION	LOE
I	CHF due to systolic dysfunction with angina or with regional wall motion abnormalities and/or scintigraphic evidence of reversible myocardial ischemia when revascularization is being considered	B
	Before cardiac transplantation	C
	CHF secondary to postinfarction ventricular aneurysm or other mechanical complications of MI	C
IIa	Systolic dysfunction with unexplained cause despite noninvasive testing	C
	Normal systolic function, but episodic heart failure raises suspicion of ischemically mediated left ventricular dysfunction	C
III	CHF with previous coronary angiograms showing normal coronary arteries, with no new evidence to suggest ischemic heart disease	C

RECOMMENDATIONS FOR USE OF CORONARY ANGIOGRAPHY IN OTHER CONDITIONS

CLASS	RECOMMENDATION	LOE
I	Diseases affecting the aorta when knowledge of the presence or extent of coronary artery involvement is necessary for management (e.g., aortic dissection or aneurysm with known coronary disease)	B
	Hypertrophic cardiomyopathy with angina despite medical therapy when knowledge of coronary anatomy might affect therapy	C
	Hypertrophic cardiomyopathy with angina when heart surgery is planned	B
IIa	High risk for coronary disease when other cardiac surgical procedures are planned (e.g., pericardiectomy or removal of chronic pulmonary emboli)	C
	Prospective immediate cardiac transplant donors whose risk profile increases the likelihood of coronary disease	B
	Asymptomatic patients with Kawasaki disease who have coronary artery aneurysms on echocardiography	B
	Before surgery for aortic aneurysm/dissection in patients without known coronary disease	
	Recent blunt chest trauma and suspicion of acute MI, without evidence of preexisting CAD	C

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CHAPTER 10

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Pericardial Disease and Hemodynamics

CHAPTER OUTLINE

NORMAL ANATOMY AND PHYSIOLOGY OF THE PERICARDIUM

■ **Anatomy:**

- Two layers: outer fibrous parietal layer and serosal visceral layer
- *Pericardial sac* between the visceral and parietal surfaces contains <50 mL of serous fluid
- Phrenic nerves run adjacent to the parietal pericardium (accounting for referred pain to the trapezius ridge due to phrenic nerve irritation during pericardial inflammation)

■ **Physiology:**

- Transmits intrathoracic pressure to the heart and affects diastolic filling; for example, during inspiration, intrapleural pressure falls; normal pericardial function will transmit a negative intrapleural pressure to the heart, to decrease intracardiac pressures and augment systemic venous return
- Barrier to infection

ACUTE PERICARDITIS

An acute inflammatory process of the pericardium affecting both layers of the pericardium.

- Epidemiology
  - Incidence of acute pericarditis has been reported at 27.7 cases per 100,000 per year and accounts for 5% of emergency room presentations for chest pain [1, 2].
  - Men aged 16–65 years are at higher risk for pericarditis than women [3].
  - 30% of patients with first episode of acute pericarditis will have recurrence within 18 months [4].
- Etiology
  - In the developed world, viruses are the most common cause of pericarditis. Tuberculosis (TB) is the most common cause of pericardial disease in the world and developing countries [5].

Etiologies [6]

Infectious causes
- Viral (most common infectious cause)
  - Enteroviruses (coxsackie, echoviruses), herpesvirues (EBV, CMV, HHV-6), adenoviruses, parvoviruses B19
- Bacterial (less common)
  - *Mycobacterium tuberculosis* (TB), *Coxiella burnetti* (Q fever), *Borrelia burgdorferi* (Lyme), *Staphylococcus aureus*. Others rare.
- Fungal (very rare)
  - *Histoplasma spp*, *Aspergillus* spp, *Blastomyces* spp, *Candida* spp
- Parasitic (very rare)
  - *Echinococcus* spp, *Toxoplasma* spp

Noninfectious causes:
- Autoimmune (common)
  - SLE, Sjögren syndrome, RA, scleroderma, systemic vasculitides, sarcoid, IBD, Adult Still's disease
- Neoplastic
  - Metastatic tumor > primary pericardial tumor (pericardial mesothelioma most common of the primary tumors)
- Metabolic
  - Uremia, anorexia nervosa, myxedema
- Traumatic/Iatrogenic:
  - Early onset: Radiation injury, thoracic injury, post-pericardiotomy
  - Delayed onset: Post-myocardial infarction, post-pericardiotomy, post-traumatic, post-procedural
- Drug-related
- Other:
  - Amyloidosis, aortic dissection, pulmonary arterial hypertension

- Clinical presentation and diagnosis
  - Clinical diagnosis with two of the following [6]:
    - **Chest pain** (>85–90% of cases)—sharp, pleuritic, improved by sitting/leaning forward, worse when lying flat and when prone; discomfort radiates to the trapezius ridge.
    - **Pericardial friction rub** (≤33% of cases)—left lower sternal border; rub = movement of pericardial surfaces against each other during cardiac motion (up to three

components: 1—ventricular systole; 2—early ventricular filling; 3—atrial contraction); variable during acute pericarditis

- **ECG changes** (up to 60% of cases)—new widespread ST elevations or PR depression. Can be localized. Reflect epicardial inflammation.
  - ECG in acute pericarditis can progress through four phases (Fig. 10-1): (1) ST segment elevation; (2) normal; (3) T wave inversions in same leads; (4) normal. These changes occur over a variable time period (e.g., weeks to months); nearly 80% patients with acute pericarditis have ST-elevations at the time of initial presentation [7]
- **Pericardial effusion** (up to 60% of cases)
- Additional supporting findings: elevated inflammatory markers (ESR, CRP, WBC) or imaging evidence of inflammation (CT, cardiac MRI)

- Clinical evaluation and examination
  - Standard evaluation should include *complete blood count* (screen for infection), *renal function* (rule out uremia), *chest x-ray* (concomitant disease), *ECG, echocardiography* (ventricular function, effusion), *cardiac troponin* (serially, to exclude significant myocardial injury/acute MI; does not correlate with prognosis), and *ESR/CRP* (to assess for disease activity)
  - Epidemiological background and a focused physical examination and history can guide further testing, including investigations for infectious causes such as TB, autoimmune conditions or malignancy.
  - Cardiac MRI or CT (for assessment of pericardial enhancement) may be used to confirm diagnosis (Fig. 10-2); identify/exclude concomitant myocarditis or myocardial infarction.

- Management
  - In patients with an identified cause, treatment should target the underlying cause
    - Bacterial pericarditis:

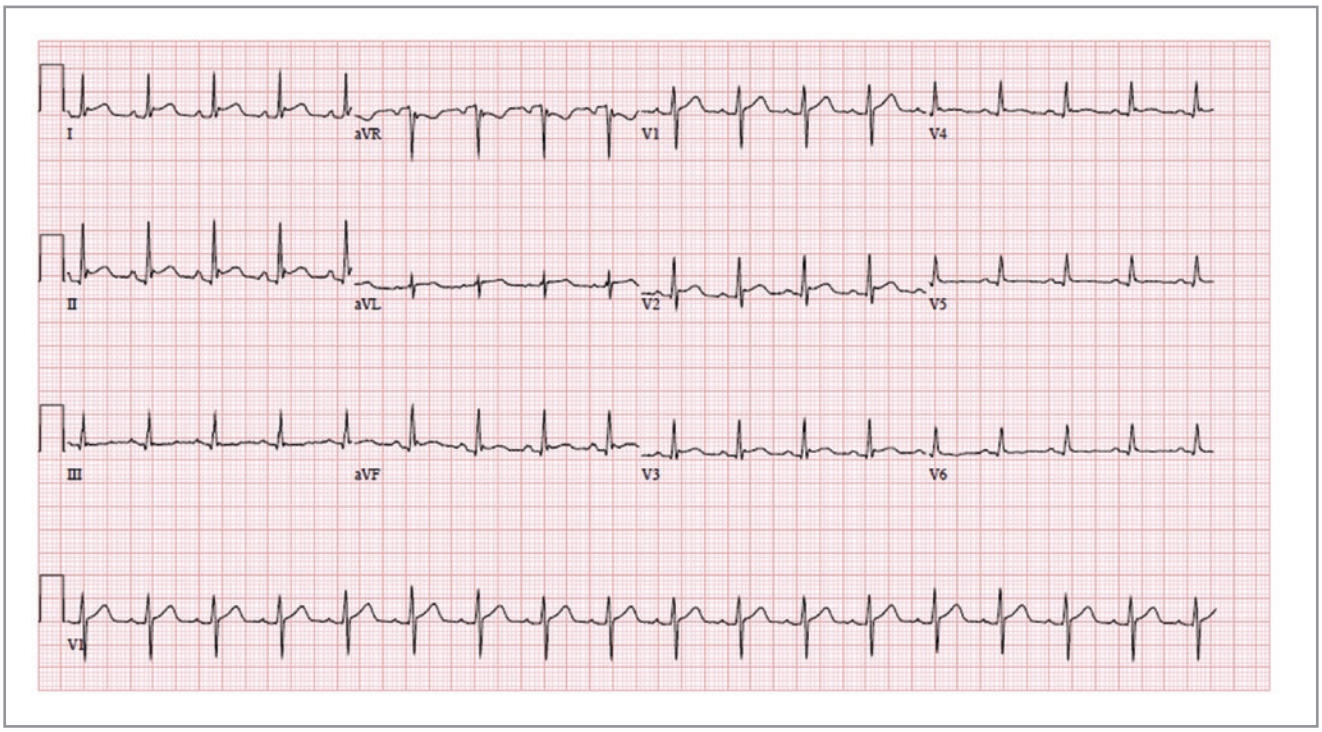
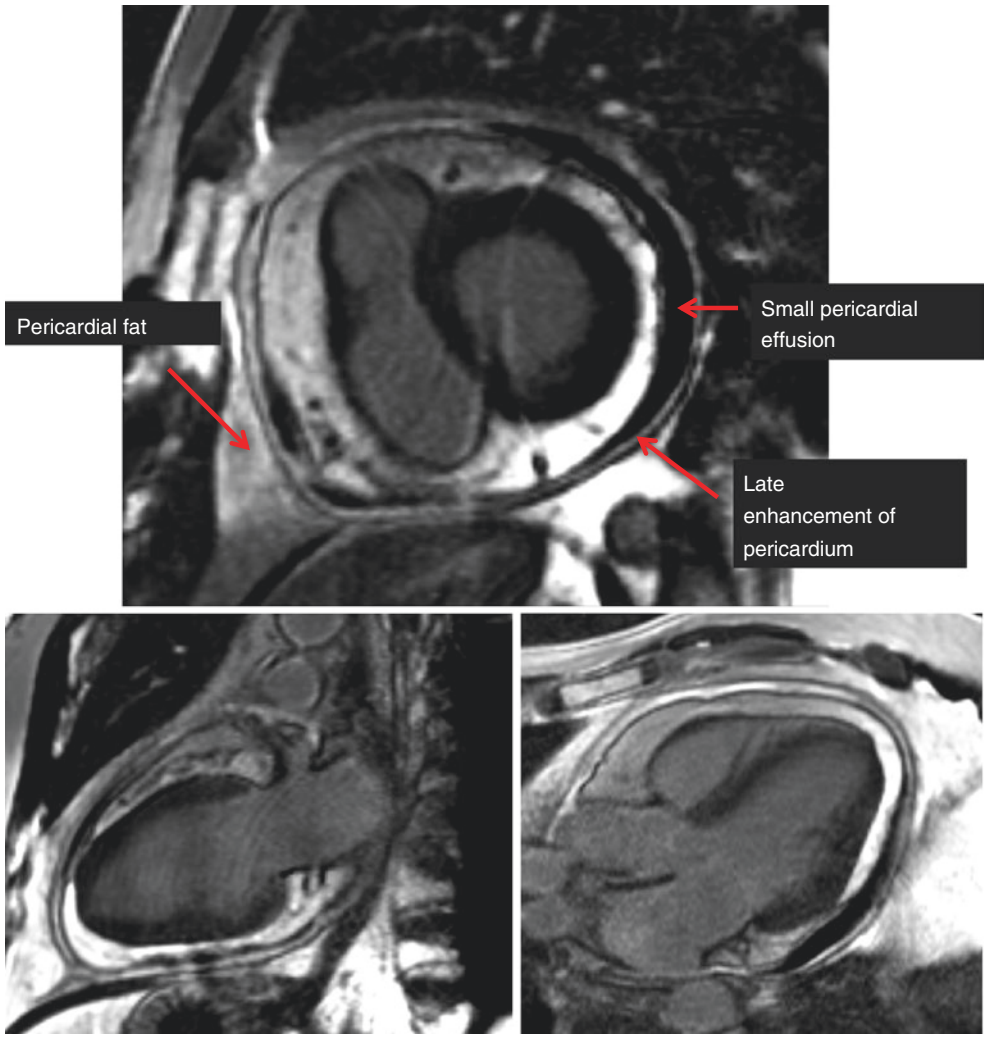


FIGURE 10-1

12-Lead electrocardiogram of an 38 year old male with pleuritic chest pain and a friction rub following an upper respiratory infection. Note sinus tachycardia with associated PR depression and diffuse ST elevation

FIGURE 10-2

Cardiac MRI of gadolinium enhancement of pericardium, consistent with inflammation (Courtesy of Dr. Ron Blankstein)



POOR PROGNOSTIC[a] RISK FACTORS

OUTPATIENT MANAGEMENT FOR LOW-RISK PATIENTS (NO RISK FACTORS)

Major [8]:
- High fever [>38 °C (>100.4 °F)]
- Subacute presentation
- Large pericardial effusion
- Cardiac tamponade
- Failure to respond to non-steroidal anti-inflammatory drugs (NSAIDs) within 7 days

Minor [9]:
- Concomitant myocarditis
- Trauma
- Oral Anticoagulation
- Immunosuppression

[a]Poor prognosis indicates pericarditis with a specific cause (autoimmune, neoplastic, tuberculous, purulent) or with increased risk of complications including recurrence, cardiac tamponade or constrictive pericarditis (Fig. 10-7)

- Purulent pericarditis: Urgent pericardiocentesis (fluid should be sent for cell count, glucose, bacterial, fungal, tuberculous studies) blood cultures should be obtained, empiric IV antibiotics should be administered. Consider intrapericardial thrombolysis (to lyse dense adhesions and facilitate drainage which may prevent persistent purulent pericarditis and subsequent development of constrictive pericarditis though data are scarce), subxyphoid pericardiotomy and rinsing of pericardial cavity and lastly pericardiectomy for persistent infection, recurrence of tamponade or progression to constriction [6].
- Tuberculous pericarditis: Pericardiocentesis (fluid should be sent for M. tuberculosis culture, PCR, fluid and serum protein, LDH, cell count, cytology, interferon gama, adenos-

ine deaminase or lysozyme assay). Antituberculosis therapy with rifampin, isoniazid, pyrazinamide and ethambutol for total of 6 months. Consideration of intrapericardial urokinase and high dose prednisolone therapy to reduce risk of constrictive pericarditis [6].

- First-line therapy for idiopathic/viral pericarditis:
  - Aspirin or non-steroidal anti-inflammatory agents (e.g., ibuprofen 600–800 mg TID, indomethacin 25–50 mg TID) with gastric protection or high dose aspirin (650–1000 mg every 8 h) in patients with pericarditis associated with MI (as NSAIDs can impair infarct healing)
    - Usual duration: 7–14 days, longer if symptoms persist
    - Relieve chest pain in up to 90%, generally within days of initiation [7].
  - Colchicine (0.6 mg daily [<70 kg] or BID [≥70 kg]) for 3 months.
- Second-line and third line therapy (if refractory to or contraindications to first-line therapy and infection excluded, consider earlier in uremic pericarditis):
  - Glucocorticoids: low dose preferred (prednisone 0.2–0.5 mg/kg/day)
  - Steroids may increase risk of recurrent pericarditis [4].
  - Patients unable to taper steroids without recurrence of pericardial symptoms should be considered for steroid-sparing therapies (e.g., immunomodulatory agents, such as azathioprine, methotrexate, anakinra, IV immunoglobulin) or intrapericardial steroid therapy [7, 10].
- Indications for pericardiocentesis: Majority of patients with uncomplicated acute pericarditis do not require pericardiocentesis. Pericardiocentesis should be considered in the following scenarios.
  - Suspected bacterial or neoplastic pericarditis
  - Pericarditis associated with cardiac tamponade (more common in malignancy, TB or purulent pericarditis; see below for management of pericardial tamponade)
  - Acute pericarditis with symptomatic moderate to large pericardial effusion and failure of anti-inflammatory therapy.
- Follow-up:
  - Physical activity should be restricted until resolution of symptoms and normalization of inflammatory markers.
  - Follow-up echocardiography is warranted if initial echocardiography demonstrated effusion (of any size) or other abnormalities.
  - Constriction develops in <1% of idiopathic and presumed viral etiologies, 2–5% of malignant and autoimmune/immune-mediated etiologies, and 20–30% of bacterial etiologies [11].
  - Incessant pericarditis lasts >4–6 weeks but <3 months without remission. Recurrent pericarditis is pericarditis that recurs after a symptom-free interval of 4–6 weeks.
  - Chronic pericarditis lasts >3 months.
  - Colchicine treatment can decrease pericarditis recurrence rates by two-thirds [4].
  - For recurrent pericarditis, first-line therapy should be extended to weeks-months with concomitant colchicine for at least 6 months.
  - Individuals with chronic or refractory pericarditis not responsive to first-line therapies are generally treated with a combination of first and second line therapy with slow glucocorticoids taper following remission or third line therapy including Azathioprine, IV immunoglobulin or biological agents such as anakinra for several months [12].

CARDIAC TAMPONADE

- Hemodynamic Principles:
  - **Impaired cardiac filling**: Once the limit of pericardial elasticity is reached, intrapericardial pressures increase as the heart competes with the pericardial volume for space. This results in impaired cardiac filling.

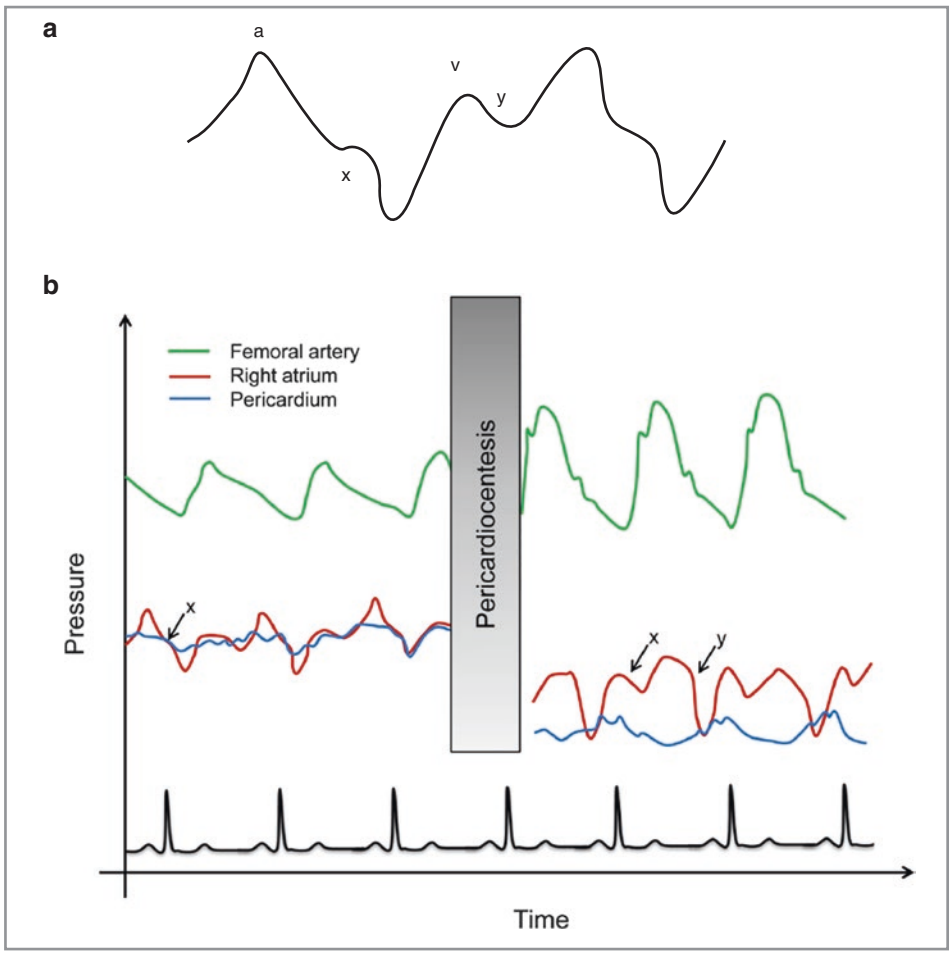


FIGURE 10-3

Hemodynamics of tamponade via right heart catheterization. (**a**) Right atrial pressure with blunted *y* descent (Courtesy of Dr. Hanna Gaggin). (**b**) Concomitant right atrial and intrapericardial pressure before and after pericardiocentesis. Note the decreased aortic pulse pressure before pericardiocentesis and the characteristic RA waveform with equalization of RA and intrapericardial pressure before relief of tamponade. After tamponade is relieved with pericardial fluid drainage, pressures normalize (Courtesy of Dr. Hanna Gaggin)

- **Ventricular interdependence**: An exaggerated reciprocal relationship between RV and LV filling and cardiac output with respiration due to pericardial constraint. (In normal physiology during inspiration, there is an increase in systemic venous return to the right heart and a decrease in pulmonary venous return to the left heart due to a greater capacitance of the pulmonary veins. In tamponade, due to pericardial constraint and reduced left ventricular volume with inspiration, the interventricular septum bulges leftward (septal shift) resulting in even further reduction in LV filling.)
- Right heart hemodynamics (Fig. 10-3):

Elevated RA pressure	Increased intrapericardial pressures impair venous return and lead to elevated RA pressure
"Blunting" or loss of the *y* descent of the right atrial pressure tracing	*y*-descent reflects early RV filling. In tamponade, very short period of initial flow from the RA into the RV in early diastole leads to "blunted" *y* descent; this is in contradistinction to constriction, see below
Diastolic equalization of pressures	<5 mmHg difference between RVEDP, LVEDP, mean RA pressure and intrapericardial pressure
Pulsus paradoxus	A >10–12 mmHg inspiratory fall in systolic blood pressure is characteristic of tamponade. Fall in systolic BP > 12 mmHg with inspiration has a sensitivity of 98% and specificity of 83% for the diagnosis of pericardial tamponade [9].

■ Caveats

- **These hemodynamic features may not be seen in cases of localized tamponade** (e.g. post-cardiac surgery with pericardial hematoma posterior to the LV). In these

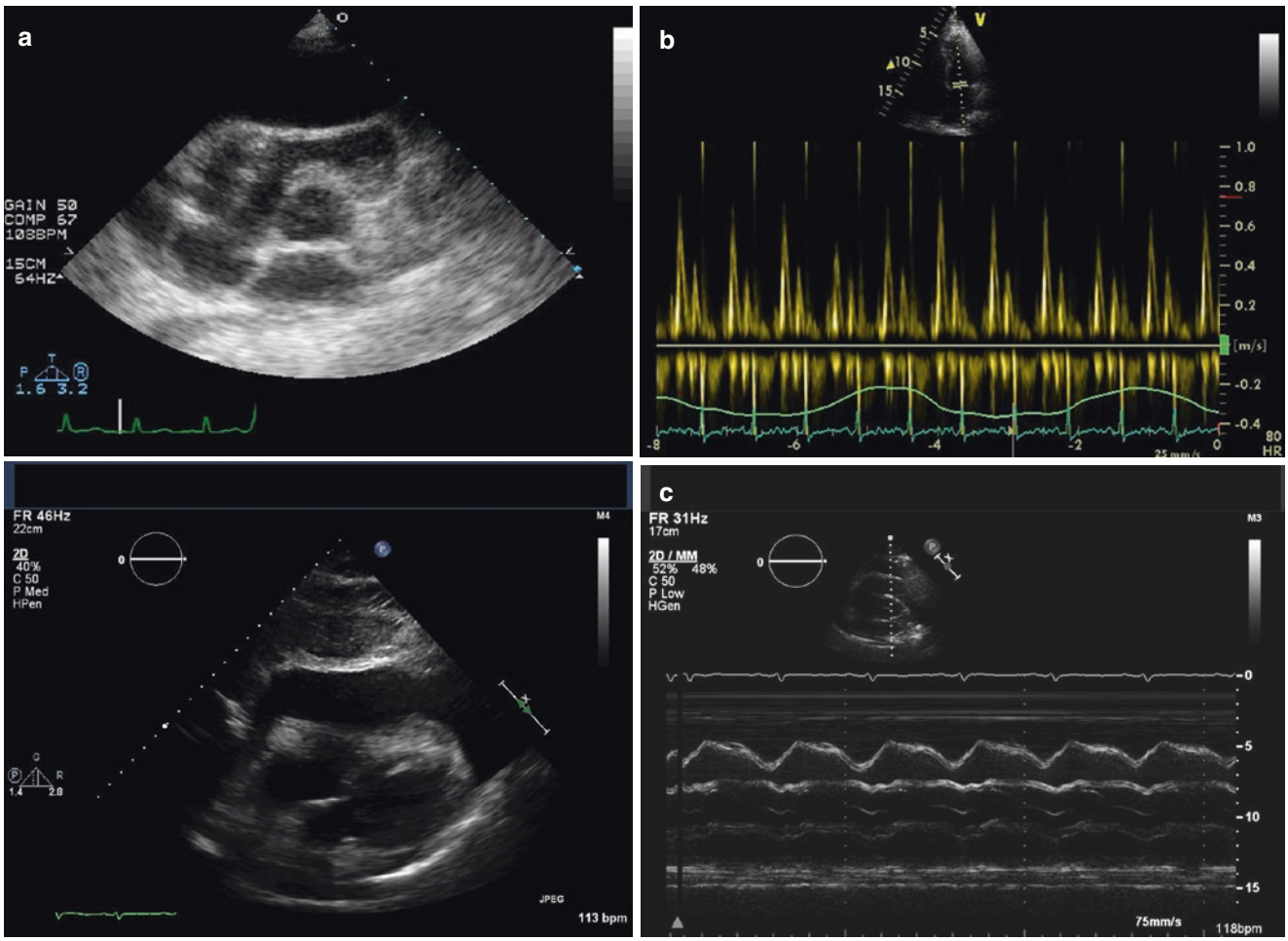


FIGURE 10-4

Echocardiography of pericardial disease (Courtesy of Dr. John Groarke, BWH). (**a**) Right ventricular collapse in two views in cardiac tamponade. (**b**) Exaggerated variation in peak E transmitral velocities with tamponade. (**c**) Cardiac tamponade by M-mode through right ventricular outflow tract. Notice M-mode evidence of diastolic inversion of the RV free wall, indicating elevated intrapericardial pressures and tamponade physiology

cases, a high index of suspicion and direct visualization of the pericardial collection (e.g., via transesophageal echocardiography or cardiac MRI, or direct surgical visualization) is required

- **Low pressure cardiac tamponade:** Can occur in the setting of hypovolemia and a fluid challenge in the catheterization laboratory would reveal typical cardiac tamponade hemodynamics.
- **Pulsus paradoxus in the absence of tamponade**: Because of ventricular interdependence severe COPD/asthma/airway obstruction, massive pulmonary embolism, RV infarction, auto-PEEP on ventilator support, pericardial constriction.
- **Tamponade without pulsus paradoxus**: Poor LV function, interatrial or interventricular septal defect, or severe aortic insufficiency due to high venous pressures and inability to alter cardiac output with inspiration.

■ Echocardiography in cardiac tamponade (Fig. 10-4 and Chap. 29 **Imaging Studies Section (Echocardiograms and Angiograms)**):

ECHOCARDIOGRAPHY IN CARDIAC TAMPONADE MAY BE ABSENT IN CASES OF LOCALIZED TAMPONADE

Right atrial inversion	RA inversion that exceeds one third of ventricular the cardiac cycle is nearly 100% sensitive and specific for clinical tamponade [13].
Right ventricular diastolic collapse (best seen in subcostal or parasternal long axis views or using M-mode)	It is often present when cardiac output has decreased by 20% without systemic blood pressure fall [10]. Moderate sensitivity (60–90%) but high specificity (85–100%). May not be seen in RVH, severe pHTN, or severe LV dysfunction.
Respirophasic variation[a] in mitral and tricuspid inflow	Peak mitral E inflow usually exceeds >30% respiratory variation [10]. Peak tricuspid E inflow exceeds >60% respiratory variation
IVC plethora	Present in >90% of patients. Defined as a dilated IVC (>2.1 cm) with <50% reduction in diameter during inspiration.
Septal shift (Inspiratory interventricular septum bulge)	Increase in RV dimension and decrease in LV dimension due to septal motion. Visualization of the pulsus paradoxus. Low specificity.

[a][(expiration−inspiration)/expiration] × 100

- Clinical evaluation and examination
  - Clinical signs/symptoms [14]:
    - Dyspnea (sensitivity 87–89%)
    - Tachycardia (sensitivity 77%)
    - Elevated jugular venous pressure (sensitivity 76%)
    - Pulsus paradoxus (sensitivity 82%). Presence of pulsus paradoxus >10 mmHg with a large pericardial effusion yields a 3.3-fold increased likelihood of tamponade
    - Cardiomegaly on chest x-ray (sensitivity 89%)
    - Narrow pulse pressure
  - *Beck's triad*: elevated jugular venous pressure, hypotension, distant heart sounds
  - ECG: In large effusions, ECG can show evidence of **electrical alternans** (a beat to beat variation in P wave or QRS amplitude owing to "swinging" motion of the heart in the thoracic cavity) or **low QRS voltage** (<5 mm in all limb leads, and <10 mm in all precordial leads; due to insulating effect of pericardial fluid on cardiac electrical activity)
- Management:
  - **Diagnosis of tamponade is clinical**. Echocardiographic and right heart hemodynamics may support the clinical evaluation
  - Urgency of management (e.g., drainage vs. observation/anti-inflammatory therapy) depends on the degree of hemodynamic significance and symptoms (e.g., severe dyspnea or breathlessness due to a large effusion that otherwise may not meet criteria for tamponade)
  - Pericardial fluid should be evaluated for leukocytes, hematocrit, protein content, cultures and gram stain (ADA level and additional PCR-based methods for TB), and cytology/flow cytometry (if lymphoma or malignancy is suspected)
  - **Pericardial effusion with tamponade**: hemodynamic stability determines management
    - Percutaneous drainage (via pericardiocentesis) may be safer than surgical drainage [15].
    - In patients with suspected aortic dissection with pericardial effusion, surgical drainage only should be performed, as percutaneous drainage could improve cardiac contractility and extend dissection (See Chap. 11 for more information on aortic dissection management).
    - Generally, a pericardial drain is left in place with attendant anti-inflammatory therapy (e.g., NSAIDs, colchicine, or steroids) and discontinued only when drain output falls below a prescribed level (e.g., 50 cc/24 h).
    - Serial echocardiography within 48 h of pericardiocentesis (generally before drain is discontinued) and within 48 h after drain discontinuation is important to assess for reaccumulation.

- **Pericardial effusions without tamponade**:
  - Initial management focused on etiology (see acute pericarditis above).
  - For larger effusions (>20 mm) without tamponade, pericardiocentesis might be considered, but an initial approach of NSAID therapy is also reasonable in certain cases, particularly with difficult-to-drain effusions.
  - Serial echocardiography and close follow-up of patients with larger effusions who are not drained is required.
- **Recurrent effusions** (e.g., malignancy-related or chronic idiopathic recurrent pericarditis) can be treated with surgical pericardiotomy or balloon pericardiotomy (in the catheterization laboratory) for poor surgical candidates.

- Cardiac tamponade—Additional considerations:
  - **Diagnostic pericardiocentesis without tamponade**
    - Given higher risk of complications with smaller effusions, **may be performed if high suspicion exists for a specific diagnosis that has been cryptic by other methods** (e.g., malignancy, TB, or bacterial infection)
    - **Purulent pericarditis** should be treated as a pericardial abscess and drained emergently; see Management of Purulent pericarditis above)
  - **Pericardial biopsy**
    - Unclear role
    - Should be performed during surgical window.
    - Considered in patients with unclear diagnosis with persistent symptoms (>3 weeks in duration) and if diagnosis would change management (e.g., malignancy, TB, bacterial infection)

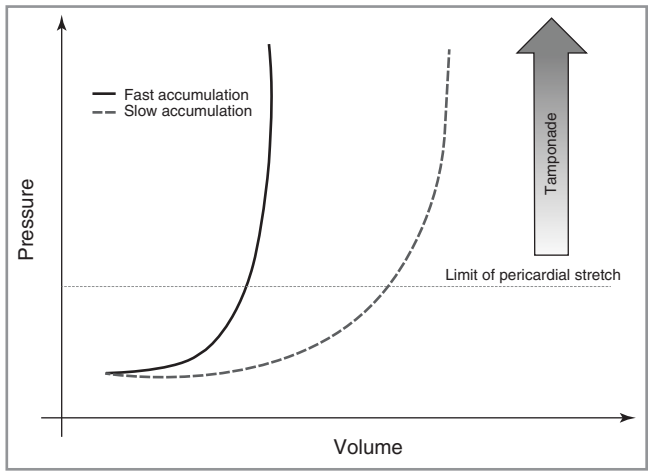
CONSTRICTIVE PERICARDITIS

Constrictive pericarditis is a result of chronic pericardial inflammation leading to pericardial scarring that limits diastolic filling. In Europe and the United States, constrictive pericarditis is most often idiopathic, post-cardiac surgery, autoimmune, or related to a non-specific viral insult. In other parts of the world, tuberculosis is the most common cause. It only rarely follows recurrent pericarditis [16].

- Constrictive pericarditis—Hemodynamics (Fig. 10-4):
  - The key hemodynamic manifestations of constriction rely on three major pathophysiologic observations:
    - Intrathoracic pressures are not clearly transmitted to the heart with constriction (**as opposed to tamponade**, where the pericardium itself is generally fairly normal)
    - Pericardial restraint creates ventricular interdependence (**similar to tamponade**) (Fig. 10-5)
    - Early diastolic filling is usually rapid, whereas later diastolic filling is limited by the presence of a stiff pericardium, which may be adherent to the surface of the heart.
  - During inspiration, the negative intrapleural pressure (which is transmitted to the pulmonary veins) results in increased venous return. Early in this process, filling is normal, but once the RV filling reaches the rigid pericardium, filling is encumbered, resulting in rise of right sided chamber pressures and development of **ventricular interdependence** (and even a pulsus paradoxus in <20% of patients with constriction)
  - Hemodynamics: The diagnosis of constriction requires the integration of clinical, hemodynamic, and imaging findings. None of these features are 100% sensitive or specific for the diagnosis of constriction. Note: typical hemodynamic findings may be absent if filling pressures are low or elevated and can be elicited with rapid volume infusion or with diuresis, respectively.

FIGURE 10-5

Pericardial restraint. Slow accumulation of pericardial fluid leads to a "give" in the pericardium, gradual increase in pericardial compliance, and a less exuberant rise in intrapericardial pressure (a higher threshold for tamponade). In rapid accumulation, the gradual increased pericardial compliance is not permitted, and tamponade ensues at a lower pericardial fluid volume (Courtesy of Dr. Hanna Gaggin)



Hemodynamic findings in constriction (Fig. 10-6)
Elevated RA pressure (generally >10 mmHg; similar to tamponade; can be provoked by fluid challenge in patients who are volume depleted)
Failure of RA pressure to fall on inspiration (hemodynamic Kussmaul sign): lack of transmission of intrapleural pressures to the RV leads to lack of increased RV filling on inspiration, and the blood cannot empty from the RA and jugular veins into the RV; this is also seen in other conditions (e.g., massive PE, RV infarction or RV failure, pulmonary hypertension)
Rapid x and *y* descents in the RA pressure tracing: initial diastolic filling is rapid in constriction, but once pericardial restraint is reached (e.g., the heart "reaches" the stiff pericardium as it tries to relax), the atrial pressure abruptly rises. The characteristic RA pressure tracing resembles a repeated "M" or "W" pattern.
Pulsus paradoxus: A >10–12 mmHg inspiratory fall in systolic blood pressure.
Equalization of RV and LV end-diastolic pressures defined as LVEDP-RVEDP < 5 mmHg (due to pericardial restraint)
"**Square root sign" (or "dip and plateau") in RV and LV diastolic pressures**: initial RV relaxation during diastole is unimpeded (leading to a rapid **dip**), but once heart "reaches" the stiff pericardium in mid-diastole, RV and LV pressures rapidly rise (leading to a **rapid rise to a plateau**)
Discordance of RV and LV pressure tracings: This is the **hallmark feature of constriction** that distinguishes this from restrictive cardiomyopathy. There is ventricular interdependence, such that the RV filling occurs at the expense of LV filling, and vice versa. On inspiration, the peak systolic RV pressure progressively rises as venous return increases, while the peak LV systolic pressure falls (**discordance**)
Pulmonary artery pressure: as opposed to restrictive cardiomyopathy, constrictive pericarditis less commonly presents with pulmonary hypertension.

– **Echocardiography:** Main findings of constriction are listed below.

Thickened, hyper-reflective pericardium (parasternal long-axis view). TEE is more sensitive and specific than TTE in assessing pericardial thickness.
Diastolic septal bounce (abnormal interventricular septal motion during early diastole reflecting motion of septum during opening of mitral and tricuspid valves)
Exaggerated respirophasic changes in mitral and tricuspid inflow (marker of ventricular interdependence as in tamponade, with >25% decrease in mitral peak E wave velocity; >40% increase in tricuspid peak E wave velocity).
Decreased systolic phase and increased atrial phase in pulmonary venous Doppler (corresponding to elevated left atrial pressures and impedance to LV filling)
High E velocity (due to rapid early diastolic filling) and **short deceleration time** (due to abrupt cessation of diastolic filling in late diastole). This is the echocardiographic equivalent of the "square root sign".
Expiratory diastolic hepatic vein flow reversal by Doppler (During expiration, there is rightward septal shift which impedes RV filling and leads to an increase in the RV diastolic pressure. This results in an expiratory increase in hepatic vein flow reversal.

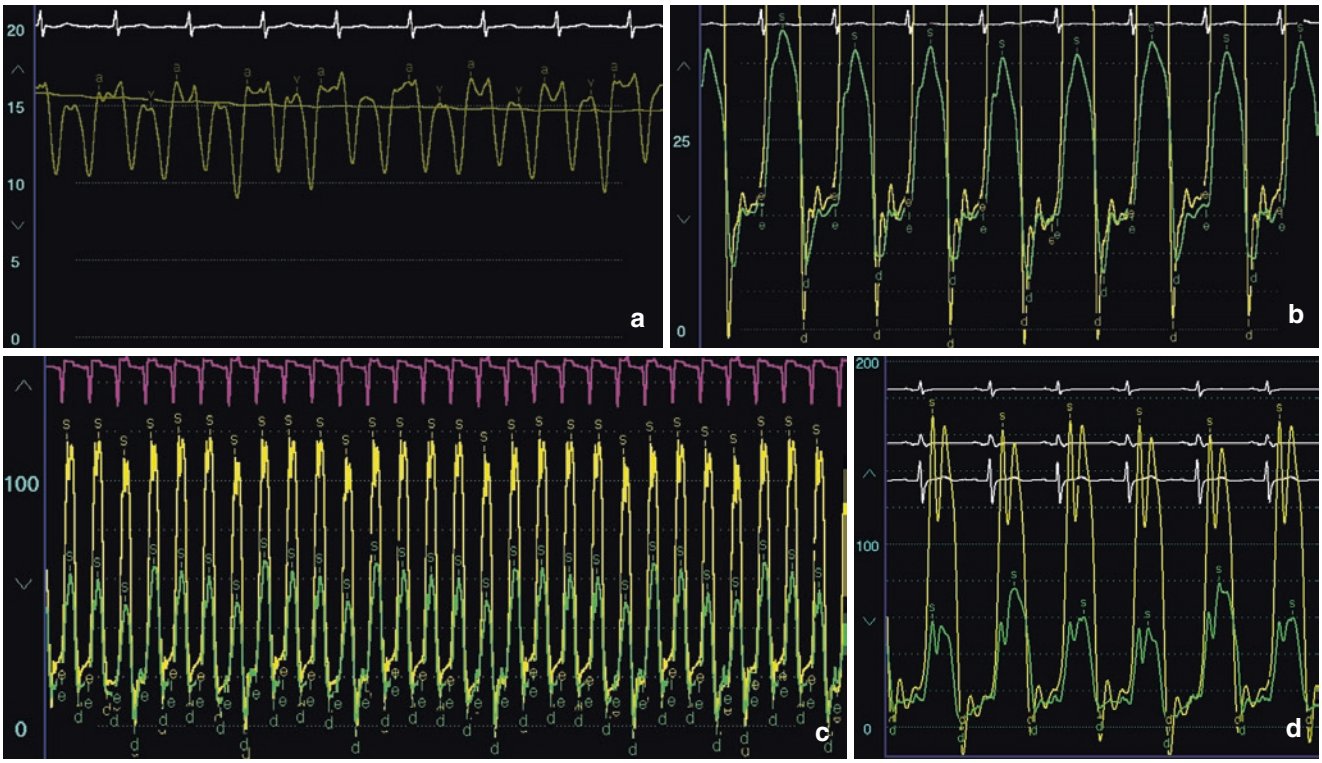


FIGURE 10-6

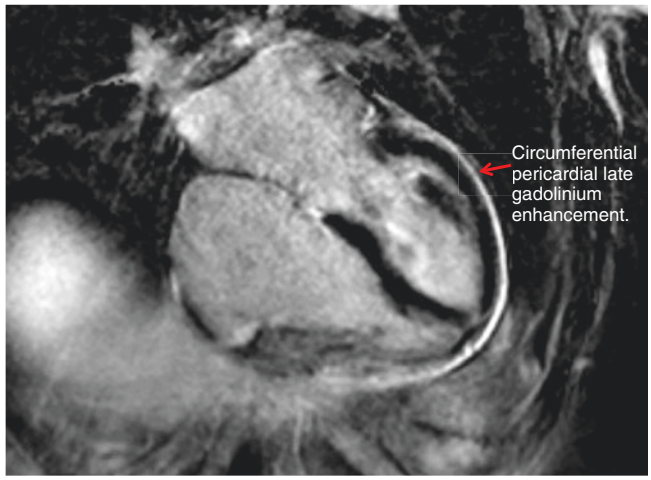
Hemodynamics of constrictive pericarditis by right and left heart catheterization (Courtesy of Dr. Michael Fifer, MGH). (**a**) Right atrial pressure. Notice rapid x and y descents in this pressure tracing (in a characteristic "W" pattern, without any significant variation in mean right atrial pressure with respiration; a Kussmaul sign). (**b**) Concomitant RV and LV pressure tracing: Notice the end-diastolic equalization of pressures (no more than 5 mmHg difference between LVEDP and RVEDP), suggesting pericardial restraint. (**c**) Concordance of LV and RV systolic pressure suggestive of restrictive cardiomyopathy (see discussion in text). (**d**) An example of discordant LV and RV pressure, suggestive of constrictive pericarditis (see discussion in text)

Preserved tissue Doppler myocardial function (e.g., E′ velocities >8 cm/s) indicating normal tricuspid and mitral annular motion. (e.g. vs. reduced motion in restrictive cardiomyopathies)
"**Annulus reversus**": mitral lateral E′ velocity is **lower** in constriction than the mitral septal E′ (opposite of a normal state, where the lateral annular velocity is higher)
Smaller ventricular volumes
Dilated IVC with diminished inspiratory collapse

- **Cardiac CT** and **chest x-ray**: primarily for the evaluation of pericardial calcification and pericardial thickness (>3–4 mm); note that up to 28% of patients in some series have pericardial constriction without evidence of a thickened pericardium (i.e. post-radiation or post-operative constriction) [17]. Thickness of pericardium is best assessed on CT which is gated to ECG
- **Cardiac MRI**: useful for imaging pericardial thickness, inflammation and scar (Fig. 10-7). Can also identify other associated myocardial disease. Specifically:
  - Pericardial thickness (>3 mm) but CT better for calcifications
  - Late gadolinium enhancement of the pericardium can be seen with pericardial inflammation and/or scar; if chronic symptoms and negative inflammatory markers → fibrosis. Increased T2 signal supports presence of inflammation.
  - Myocardial tagging to identify pericardial adhesions—i.e. absence of independent motion between pericardial surface and myocardium
  - Late gadolinium enhancement and ventricular function (to investigate restrictive cardiomyopathy)

FIGURE 10-7

Cardiac MR demonstrating pericardial late gadolinium enhancement in a patient with constrictive pericarditis



- Similar to echocardiography, MRI also assesses for "septal bounce", atrial size, IVC size

- **Restriction or constriction?**
  - Common clinical scenario (and likely to be represented on the Boards)
  - Features of restriction
    - **No ventricular interdependence** (e.g., concordance in RV/LV filling; lack of respiratory septal shift, lack of pulsus paradoxus).
    - **Evidence of abnormal myocardium** (e.g., decreased tissue Doppler E' velocities, valvular regurgitation and pulmonary hypertension, myocardial scar by cardiac MRI)
    - **Left heart failure symptoms predominate**
  - Table shows some salient features that help differentiate these two entities.

CHARACTERISTICS	CONSTRICTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY
Physical examination	■ Right-sided heart failure signs predominate (e.g., ascites, edema) ■ Pericardial knock ■ Kussmaul sign ■ Pulsus paradoxus	■ Evidence of pulmonary edema (left heart failure) ■ Kussmaul sign ■ S3
Electrocardiogram	■ Generally normal ECG but may see atrial fibrillation	■ Low voltage can be present ■ AV block ■ Atrial or ventricular arrhythmias ■ Pseudoinfarction
Hemodynamics	■ Discordance of LV/RV systolic pressure ■ LVEDP-RVEDP < 5 mmHg ■ RVEDP/RVSP < 1/3 ■ Ventricular interdependence ■ No pulmonary hypertension	■ Concordance of LV/RV systolic pressure ■ LVEDP-RVEDP > 5 mmHg ■ RVEDP/RVSP > 1/3 ■ Pulmonary hypertension (>55 mmHg)
Therapy	■ Diuretics, anti-inflammatory therapy in those with markers of inflammation (elevated CRP, imaging evidence of pericardial inflammation) ■ Pericardiectomy	■ Diuretics, cardiac transplantation

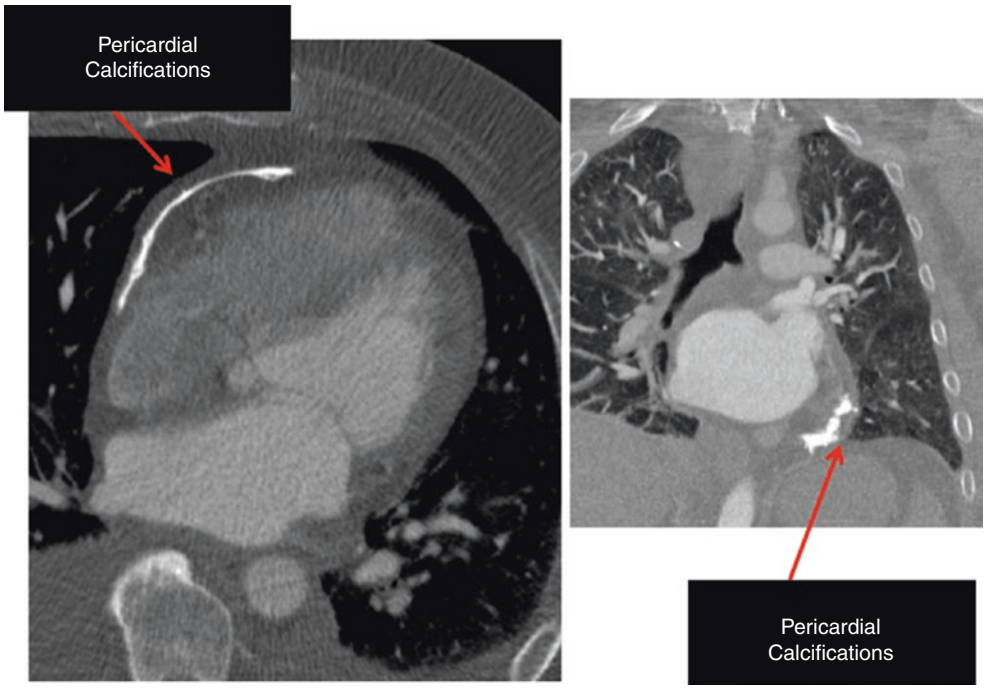


FIGURE 10-8

Pericardial calcifications demonstrated by cardiac CT

- **Effusive-constrictive pericarditis**: Pericardial effusion and constriction can co-exist (e.g., in malignancy-associated pericardial disease); although initial hemodynamics may appear consistent with tamponade physiology, a failure of the right atrial pressure and its waveform to normalize (defined as decrease in right atrial pressure by 50% or to <10 mmHg) after drainage of an associated pericardial effusion suggests overlying **constriction** (Fig. 10-8) [18].
- **Constrictive pericarditis—Management**
  - Early post-operative "constriction" is likely to recover within weeks-months of initial diagnosis (e.g., with anti-inflammatory therapy), and **constriction should not be diagnosed in the acute or immediate post-operative setting**
  - The mainstay of initial management of constrictive pericarditis is **relief of congestive symptoms** with judicious diuretic therapy
  - With diuretic-refractory symptoms or low-output symptoms, pericardiectomy should be considered
  - Mortality rate for pericardiectomy is proportional to functional status at the time of surgery (in general a high peri-operative mortality between 5 and 15%)
  - Careful selection for and timing of surgery critical; early pericardiectomy in medically refractory patients preferred; patients with advanced end-organ dysfunction (e.g., renal failure, malabsorption syndromes, poor nutrition, compromised perfusion) or overlying restrictive cardiomyopathy (e.g., with radiation or other myocardial diseases) fare poorly post-operatively.

PERICARDIAL MASSES

- **Pericardial tumors**
  - **Primary (rare, often benign)**
    - **Benign:** Teratoma, fibroma, lipoma, hemagioma
    - **Malignant:** Mesothelioma and angiosarcoma are most common primary tumor.
  - **Metastatic (most common):** Lymphoma, melanoma, lung or breast carcinoma
- **Pericardial cysts**
  - Uncommon and generally benign. Do not communicate with the pericardial space.

- Asymptomatic cysts can be observed, symptomatic cysts may require aspiration or surgical excision.

- **Pericardial diverticula**
  - Rare out-pouching of the parietal pericardium, most often at the costophrenic angle. Unlike a cyst, it communicates with the pericardial space and may vary in size.
    - Asymptomatic lesions are observed, symptomatic lesions may require surgical resection

PRESSURE-VOLUME LOOPS

- **Standard Pressure-volume (PV) loop** (Fig. 10-9)
  - One cardiac cycle consists of four elements:
    - QRS corresponds to Point A (Fig. 10-9), indicating the end of diastole and the beginning of systole
      - **Systole**
        - Isovolumic contraction: between Points A (mitral valve closure) and B (aortic valve opening)
        - Ejection: between Points B (aortic valve opening) and C (aortic valve closure)
      - **Diastole**
        - Isovolumic relaxation: between Points C (aortic valve closure) and D (mitral valve opening)
        - Ventricular filling: between D (mitral valve opening) and A (mitral valve closure)
  - Additional parameters of the PV loop
    - **Stroke volume (SV):** EDV-ESV
    - **Ejection Fraction (EF):** SV/EDV
    - **Stroke Work:** represented by the area within the pressure volume loop. Estimated by multiplying SV by mean arterial pressure (MAP).

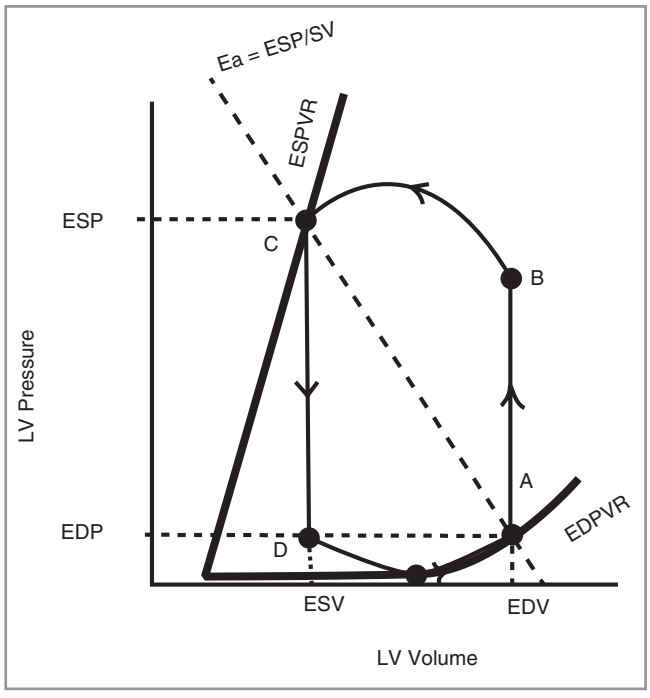


FIGURE 10-9

Normal pressure volume loop (See discussion in text)

- **Arterial Elastance (Ea):** ESP/SV, arterial afterload.
- **End-systolic pressure volume relationship (ESPVR):** Is a linear relationship that represents the contractile properties of the ventricle. The slope of the ESPVR (end-systolic elastance, Ees; Fig. 10-9) is a load independent measure of contractility.
- **End-diastolic pressure volume relationship (EDPVR):** Is a curvilinear relationship that represents stiffness of the ventricle when the myocardium is relaxed, a measure of lusitropy.

- **Pressure-volume loop response**
  - Preload (Fig. 10-10a):
    - Increase in end-diastolic volume without changes in afterload or contractility results in increased stroke volume. A decrease in end-diastolic volume results in a decrease in stroke volume.
  - Afterload (Fig. 10-10b):
    - Increasing afterload without changes in preload or contractility will increase LV pressure but decrease stroke volume. Conversely, decreasing afterload would decrease LV pressure but increase stroke volume.
  - Contractility (Fig. 10-10c):
    - Increasing contractility (without changes in afterload or preload would increase blood pressure and stroke volume. Decreasing contractility would decrease blood pressure and stroke volume.

- **Pressure-volume loop in heart failure**
  - *Heart failure with reduced ejection fraction (HFrEF)*—Fig. 10.11a
    - LV remodeling results in increased LV volume with poor contractility. Afterload may be increased compared to normal and SV is decreased. The PV loop is shifted to the right compared to normal.
    - Afterload reduction results in decreased LV pressure and increased stroke volume.
  - *Heart failure with preserved ejection fraction (HFpEF)*—Fig. 10.11b
    - Ventricular (EDPVR) and arterial stiffening are increased and the stroke volume is decreased. Blood pressure is decreased.
    - Afterload reduction results in a decrease in LV pressure and slight increase in stroke volume
    - Reduction in preload results in hypotension while increases in preload lead to pulmonary congestion due to increased diastolic pressures.

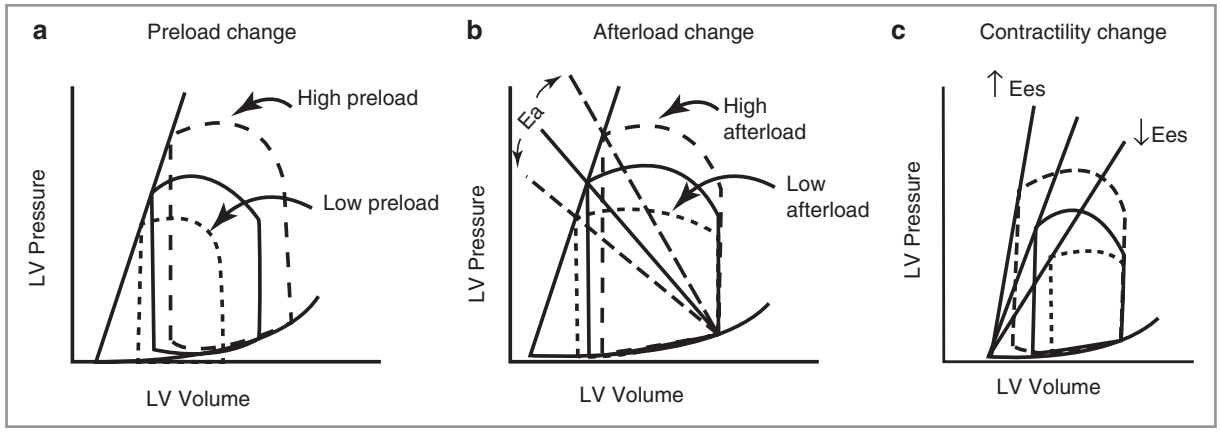
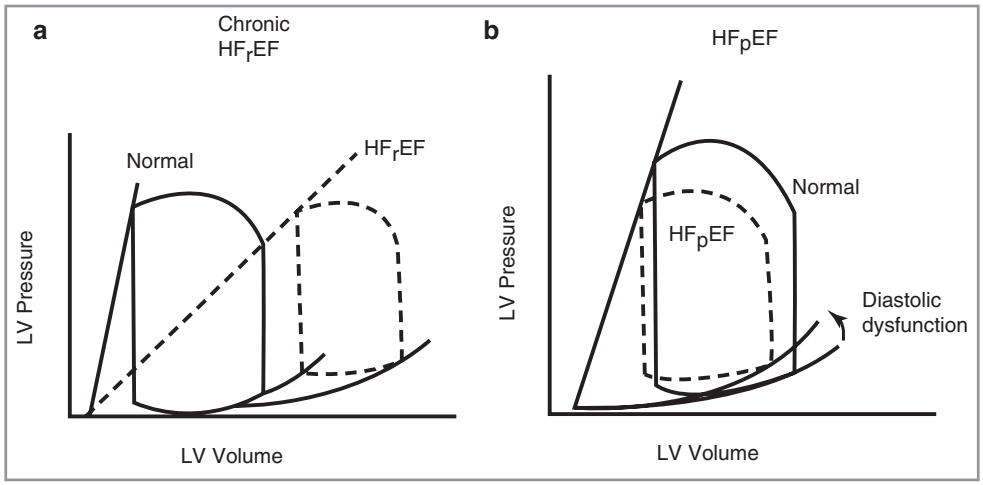


FIGURE 10-10

Pressure volume loop response to (**a**) changes in preload, (**b**) changes in afterload and (**c**) changes in contractility

FIGURE 10-11

Pressure volume loop in (**a**) chronic heart failure with reduced ejection fraction and (**b**) heart failure with preserved ejection fraction



Questions and Answers

1. A 38-year-old male with a history of self-limited viral upper respiratory infection 1 week prior to admission presents with pleuritic chest pain. Physical examination demonstrates a blood pressure of 110/60 mmHg, a heart rate of 105 bpm and a three-component friction rub. ECG shows diffuse ST elevations with the exception of ST depression in lead AVR. Initial WBC is 12 K/μL, CRP is 143.2 mg/L, ESR is 101 mm/h and high sensitivity troponin T concentration is 30 ng/L (reference normal <15 ng/L). Echocardiogram shows a small pericardial effusion without evidence of cardiac tamponade. What is the best therapeutic approach?
   (A) High dose NSAIDs and colchicine
   (B) NSAID therapy alone
   (C) Emergent pericardiocentesis
   (D) High dose prednisone
   Answer: (A)

   This patient has evidence of acute pericarditis based on pleuritic chest pain, friction rub, typical ECG findings and elevated inflammatory markers. First line therapy includes treatment with NSAIDs and colchicine. Colchicine reduces risk of recurrent pericarditis. Treatment with corticosteroids is reserved for cases that are refractory to first line therapy or for specific indications such as systemic inflammatory diseases or renal failure. Pericardiocentesis is not indicated in the absence of cardiac tamponade.

2. A 78-year-old female with hypertension and hyperlipidemia presents to the emergency room with acute onset substernal chest pain and is identified to have an inferior S-T segment elevation myocardial infarction. She undergoes emergency coronary angiography with uncomplicated deployment of a drug eluting stent to the right coronary artery via right femoral artery access. Left ventriculography demonstrates preservation of left ventricular function. She is admitted to cardiac intensive care unit for further monitoring. Six hours post procedurally, she is noted to have persistent blood pressures of 70/40 mmHg for which vasopressor support is initiated. Physical examination is otherwise notable for elevated jugular venous pressures, clear lungs, and normal heart sounds. Her right femoral access site is without evidence of bruit or hematoma. What is the next step in management?
   (A) Urgent computed tomography of the abdomen/pelvis
   (B) Dobutamine administration for cardiogenic shock
   (C) Observation
   (D) Emergent transthoracic echocardiography
   (E) Right heart catheterization
   Answer: (D)

   Post-procedural hypotension should include a high index of suspicion for tamponade from either iatrogenic or mechanical complications of myocardial infarction. In the setting of a benign groin exam, mechanical complications of myocardial infarction and iatrogenic complications need to be considered as explanations for hypotension. The acute presentation and urgent revascularization argues against a mechanical complication. An emergent transthoracic echocardiogram can help identify a pericardial effusion, in this case related to iatrogenic coronary perforation at the time of revascularization.

3. A 67 year-old male is admitted for pericarditis and pleuritisof unclear etiology. He completes a 6-week course of NSAIDs and is prescribed a 3-month course of colchicine. 2-months into his colchicine course, he is admitted with unexplained volume overload, which responds to diuresis, and is discharged. He is readmitted 2-weeks later with recurrent heart failure. A transthoracic echocardiogram revealed preserved biventricular function with a diastolic septal bounce. There is no hemodynamically significant valvular disease. There is no pericardial effusion. He has no evidence of elevated central venous pressure or peripheral edema and feels well. What is the appropriate next step in management?
   (A) Observation
   (B) Cardiac MRI evaluate for evidence of constrictive pericarditis
   (C) Steroid therapy
   (D) Simultaneous right and left heart catheterization
   Answer: (B)

Although a rare complication of idiopathic pericarditis, constrictive physiology must be considered in patients with recurrent heart failure following a pericarditis presentation. Cardiac MRI allows for non-invasive assessment of pericardial thickness and pericardial tethering. Cardiac MR can help provide better cardiac visualization, particularly in those patients with nonspecific echocardiographic findings. In the event non-invasive testing is inconclusive and a high index of clinical suspicion remains, simultaneous right and left heart catheterization remains the diagnostic gold standard.

4. Right heart catheterization in a dyspneic 78-year-old patient with prior mantle radiation shows:

Central venous pressure	15 mmHg
Right ventricular pressure	55/20 mmHg
Pulmonary arterial pressure	55/22 mmHg
Pulmonary capillary wedge pressure	20 mmHg
Left ventricular pressure	120/30 mmHg

Echocardiography shows normal LV function without any significant wall motion abnormalities or left ventricular hypertrophy. LV and RV pressures were not simultaneously recorded. What finding on cardiac imaging would be consistent with the primary suggested etiology of these hemodynamics?

(A) Transmural late gadolinium enhancement of the anterior wall on cardiac MRI
(B) A septal tissue Doppler myocardial velocity >10 cm/s
(C) Large cardiac silhouette on chest x-ray
(D) Lack of septal bounce and lack of change in transmitral peak E wave velocity with respiration

Answer: (D)

The hemodynamic profile presented above is consistent with elevated biventricular filling pressures, pulmonary hypertension, and lack of diastolic equalization of filling pressure. While this could be consistent with valvular heart disease or systolic dysfunction, these etiologies are unlikely given the normal echocardiogram. These findings could be consistent with restrictive cardiomyopathy (elevated CVP > 10 mmHg; RVEDP/RVSP > 1/3 with PA pressure > 50 mmHg). Choice (A) represents a large anterior infarct, which is not likely given the absence of wall motion on the echocardiogram. (B) represents normal (or even supranormal) myocardial function, which is unlikely in RCM. (C) represents either a dilated cardiomyopathy or pericardial effusion, both excluded by echocardiography. (D) represents characteristic findings on TTE for RCM.

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CHAPTER 11

JEREMY D. JACOBSON AND IDO WEINBERG

Venous Thromboembolism

CHAPTER OUTLINE

ABBREVIATIONS

AC	Anticoagulation
BNP	Brain natriuetic peptide
CDT	Catheter directed therapy
CT	Computed tomography
CTPA	Computed tomography pulmonary angiography
CV	Cardiovascular
DVT	Deep venous thrombosis
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
HTN	Hpertension
ICU	Intensive care unit
IV	Intravenous
IVC	Inferior vena cava
LE	Lower extremity
LMWH	Low molecular weight heparin
LV	Left ventricle
MR	Magnetic resonance
OAC	Oral anticoagulant
PE	Pulmonary emoblism
PH	Pulmonary hypertension
PTS	Post thrombotic syndrome
RBBB	Right bundle branch block
RV	Right ventricle
SQ	Subcutaneous
UE	Upper extremity
V/Q	Ventilation perfusion
VKA	Vitamin K antagonist

VENOUS THROMBOEMBOLISM (VTE)

Epidemiology

- 1–2 per 1000 person-years [1].
- Responsible for over 100,000 deaths annually in the United States.
  - Pulmonary embolism third leading cause of cardiovascular (CV) death following stroke and heart attack.
- VTE recurrence after unprovoked events is very high with rates around 30% at 5 years post discontinuation of anticoagulation [2].

Risk Factors

- **Acquired ("CHIMP TAP")**
  - **C**entral venous catheters
  - **H**eparin induced thrombocytopenia
  - **I**mmobilization
  - **M**alignancy
  - **P**rior history of VTE
  - **T**rauma
  - **A**ntiphospholipid syndrome
  - **P**regnancy/hormone replacement
- **Inherited Thrombophilia**
  - Examples include: Factor V Leiden (most common), Prothrombin gene mutation, Protein S and C deficiency, Antithrombin deficiency.
- **Anatomic Compression**
  - Iliac vein compression syndrome ("May-Thurner syndrome") → left common iliac vein compression by the right common iliac artery.
  - Thoracic outlet syndrome → compression of subclavian vein due to combination of factors: cervical rib abnormality, muscular anomalies, or injury to neck. Termed "Paget-Schroetter" if effort induced.
  - Compression by a mass (e.g. hematoma or tumor).

Presentation

- ***History*** → Risk factors as above, asymmetric lower extremity swelling, leg pain, sudden onset pleuritic chest pain and/or dyspnea, hemoptysis, cough, syncope (seen in massive PE)
- ***Physical Exam*** → Tender/swollen/erythematous lower extremity, tachypnea, tachycardia, hypoxia, loud S2 (sign of pulmonary HTN), elevated jugular venous pressure (associated with RV dysfunction/HF)
- ***Laboratory Findings*** → Elevated D-dimer (high sensitivity test i.e. good to "rule out" DVT/PE), elevated cardiac biomarkers troponin and brain natriuretic peptide (BNP), increased alveolar-arterial gradient
- ***ECG*** → Sinus tachycardia (most common), RBBB, "S1Q3T3"
- ***Imaging***:
  - ***Chest X-ray*** → most often unremarkable
    - "Westermark sign"—analogous to filling defect seen on CT with sharp cutoff of vasculature distal to embolism
    - "Hampton's Hump"—wedge shaped consolidation in distal lung due to pulmonary infarction

- ***Echocardiography*** → Dynamic study that allows for quick assessment of cardiac involvement, specifically signs of right heart strain and/or intracardiac thrombus.
  - "McConnell's sign"—RV free wall akinesis and sparing of the apex, which is often hyperdynamic
  - RV dilatation
  - Pulmonary hypertension
  - Interventricular septal flattening due to RV pressure overload
  - Identification of "clots in transit" which represent clots in the right sided chambers that have yet to embolize into the pulmonary arteries
  - Identification of patent foramen ovale or other intracardiac shunts that can lead to paradoxical embolism
- ***Venous Duplex Ultrasonography*** → Imaging modality of choice for diagnosis of DVT.
  - Non-compressibility is the ultrasonographic sign most specific for the diagnosis of DVT
  - Allows for visualization and extent of thrombus
  - Not adequate for assessing clot age (acute vs. chronic)
- ***CT and MR Venography*** → Alternative imaging modality for diagnosis of DVT.
  - Generally reserved for cases with suspicion for iliac vein and/or IVC thrombus or when there is an inability to perform ultrasonography.
- ***CT Pulmonary Angiography (CTPA)*** → Imaging modality of choice for diagnosis of PE and in some centers includes scanning of the proximal lower extremity veins. It has replaced invasive pulmonary angiography as the gold standard for diagnosis.
  - Contrast filling defect in pulmonary artery confirms diagnosis of PE
  - Evidence of right heart strain: RV/LV size >0.9, reflux of contrast within the IVC
- ***Ventilation Perfusion (V/Q) Lung Scan*** → Alternative imaging modality for diagnosis of PE
  - Nuclear medicine scan that uses scintigraphy
  - PE will demonstrate perfusion defect with normal ventilation (assuming no other lung abnormality)
  - Often used when contraindication to CTPA (i.e. contrast allergy, renal failure)

DEEP VENOUS THROMBOSIS (DVT)

Definitions

a. **Proximal DVT**: Inferior vena cava, common/internal/external iliac, common/deep/femoral, popliteal
b. **Distal DVT (below knee/calf)**: Anterior tibial, posterior tibial, peroneal, and muscular (gastrocnemial, soleal)
c. **Upper Extremity DVT**: Superior vena cava, brachiocephalic, internal jugular, subclavian, axillary, brachial, radial, and ulnar
   i. <10% of all DVT
   ii. Usually associated with indwelling catheters or pacemakers
d. **Superficial Venous Thrombosis**:
   i. **Lower Extremity** → Great/small saphenous (above and below the knee)
   ii. **Upper Extremity** → Cephalic, basilic, median cubital

TABLE 11-1

WELLS' SCORE FOR DVT[a]

CLINICAL FEATURE	SCORE
Active cancer (treatment ongoing or within 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recent bedridden for more than 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely as or greater than that of DVT	−2

Wells PS, Lancet. 1997 Dec 20–27;350(9094):1795-8
[a]In patients with bilateral symptoms, the more symptomatic leg is used
Clinical Probability: Low = 0, Intermediate 1–2, High >2

Diagnosis

■ **Assessment of pre-test probability is an essential first step as this will determine the type of testing (if any) going forward. Clinical judgement in conjunction with a validated risk assessment tool (see below) should be utilized to assess the likelihood of DVT** [3, 4].

a. Clinical suspicion i.e. risk factors, concerning presentation
b. Wells' Score for DVT (see Table 11-1)
c. Algorithm for Suspected DVT (see Fig. 11-1)

(See section "Treatment of Deep Vein Thrombosis and Pulmonary Embolism" for treatment)

PULMONARY EMBOLISM (PE)

Definitions

a. **Pulmonary Embolism**—blood clot originating most commonly from the deep veins of the lower extremities with embolization and occlusion to varying degrees of the pulmonary arteries.

i. **Low Risk PE**—Clinically stable, no signs of RV dysfunction or elevated cardiac biomarkers, PE Severity Index score < 85 (predicts 30-day mortality risk in patients with confirmed PE)
ii. **Submassive PE**—Signs of RV dysfunction on CT or ECHO or positive biomarkers of injury (cardiac enzymes and/or BNP) WITHOUT hypotension
iii. **Massive PE**—Signs of RV dysfunction same as in submassive PE but with hemodynamic instability, defined as a systolic arterial blood pressure <90 mmHg for >15 min

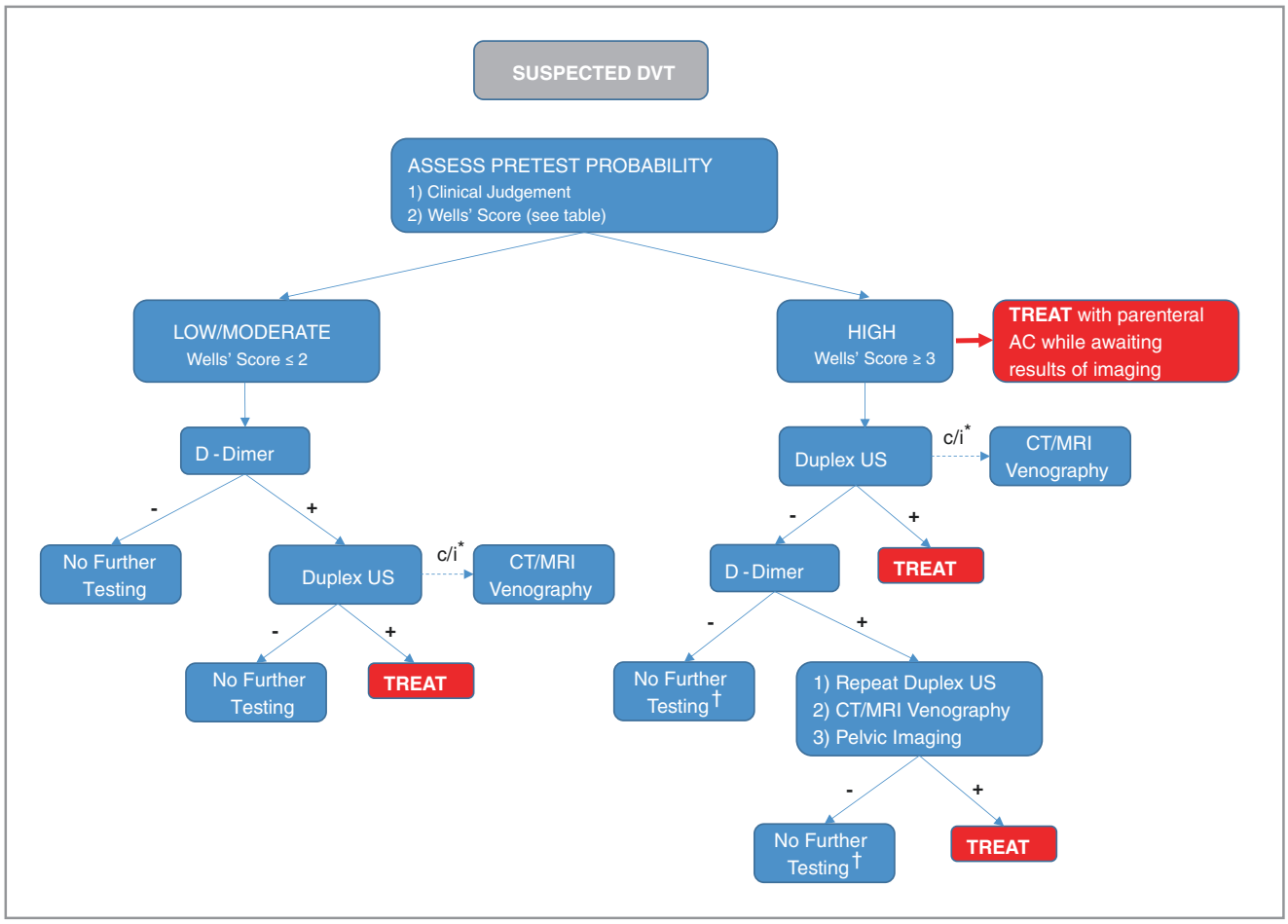

FIGURE 11-1

Algorithm for diagnosis of suspected deep vein thrombosis. Asterisks indicate casts, open wounds; dagger indicates if suspicion still high, consider repeat duplex US, CT/MRI venography, or pelvic imaging. Otherwise alternative diagnoses should be pursued. *C/I*, contraindication; *CT*, computed tomography; *DVT*, deep vein thrombosis; *MRI*, magnetic resonance imaging; *US*, ultrasound

Diagnosis

■ **Pre-test probability assessment is an essential first step as this will dictate the type of testing (if any) going forward. Clinical judgement in conjunction with a validated risk assessment tool (see below for several such tools) should be utilized to assess the likelihood of PE** [5, 6, 7].

a. *Clinical suspicion* i.e. risk factors, concerning presentation
b. *Wells' Score* for PE (see Table 11-2)
c. *Revised Geneva Score* (see Table 11-3)
d. *Pulmonary Embolism Rule Out Criteria (PERC).* If suspicion for PE low can use criteria below. One point for each criterion. If score = 0 no further testing warranted.

TABLE 11-2

WELLS' SCORE FOR PE DIAGNOSIS

CLINICAL FEATURE	SCORE
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate greater than 100	1.5
Immobilization or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment, treated in the last six months or palliative)	1

Wells PS, Thromb Haemost. 2000 Mar;83(3):416–20
Clinical Probability: Low <2, Intermediate 2–6, High >6

TABLE 11-3

REVISED GENEVA SCORE

CLINICAL FEATURE	SCORE
Age >65	1
Prior DVT or PE	3
Surgery or Fracture <1 month prior	2
Active Malignancy	2
Unilateral Leg Pain	3
Hemoptysis	2
HR 75–94 beats/min	3
HR ≥95 beats/min	5
Pain on deep palpation of lower limb and unilateral edema	4

Le Gal G, Ann Intern Med. 2006 Feb 7;144(3):165–71
Clinical Probability: Low 0–3, Intermediate 4–10, High >10

1. age < 50 years
2. pulse < 100 beats min
3. $SaO_2 \geq 95\%$
4. no hemoptysis
5. no estrogen use
6. no surgery/trauma requiring hospitalization within 4 weeks
7. no prior venous thromboembolism
8. no unilateral leg swelling

e. Algorithm for Suspected PE (see Fig. 11-2)

(See section "Treatment of Deep Vein Thrombosis and Pulmonary Embolism" for Treatment)

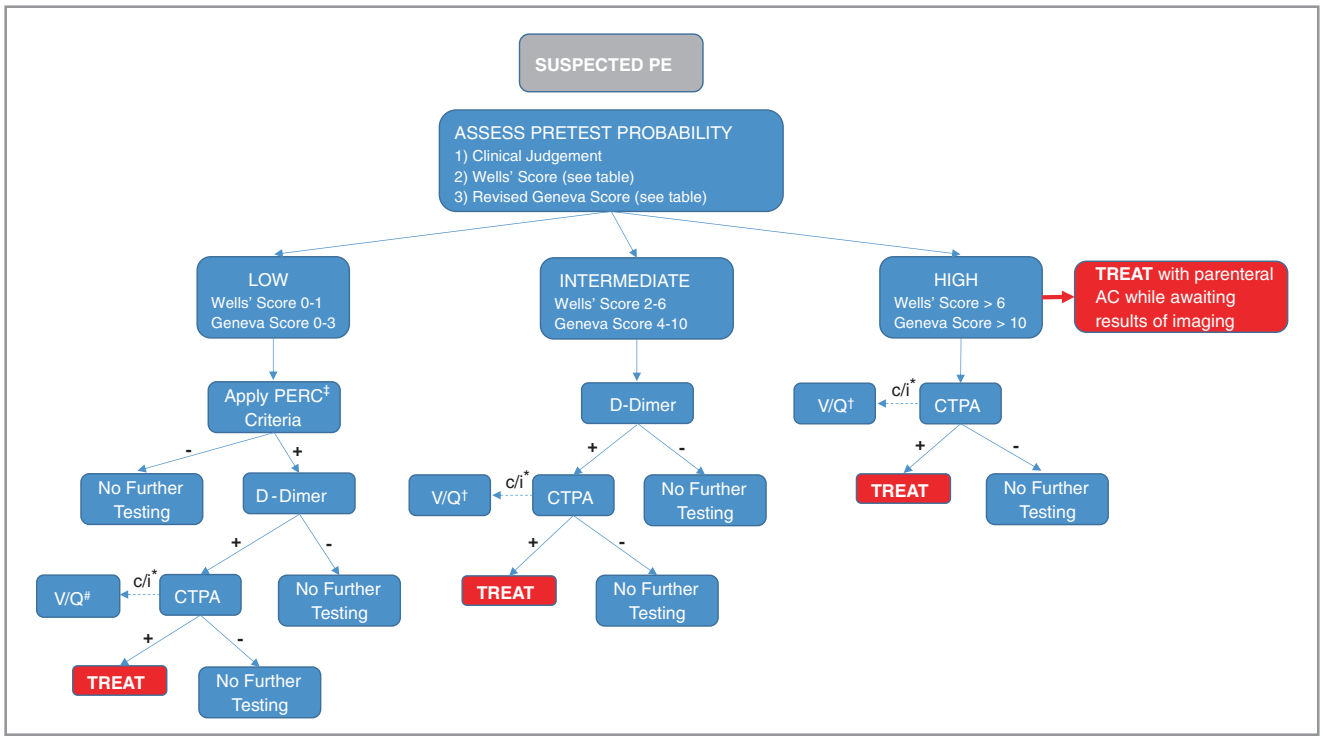

FIGURE 11-2

Algorithm for diagnosis of suspected pulmonary embolism. Asterisks indicate contraindications: contrast allergy, severe renal failure. Dagger indicates if V/Q indeterminate and suspicion for deep vein thrombosis, duplex ultrasound of lower extremities is recommended. In cases where suspicion for PE is high the risk of performing CTPA (i.e. worsening renal failure) should be weighed with the benefit of confirming diagnosis. Double dagger indicates Pulmonary Embolism Rule Out Criteria (PERC): age < 50 years; pulse < 100 beats/min; $SaO_2 \geq 95\%$; no hemoptysis; no estrogen use; no surgery/trauma requiring hospitalization within 4 weeks; no prior venous thromboembolism (VTE); no unilateral leg swelling. Negative = no criteria met. Positive = one or more criteria met. *C/I*, contraindication; *CTPA*, computed tomography pulmonary angiography; *PE*, pulmonary embolism; *PERC*, pulmonary embolism rule out criteria; *V/Q*, ventilation perfusion lung scan

TREATMENT OF VTE

- In patients with a **HIGH** probability of acute VTE parenteral anticoagulation is recommended while awaiting results of diagnostic imaging [3].
- In patients with a **MODERATE** probability of acute VTE parenteral anticoagulation is recommended if results of diagnostic imaging are expected to be delayed >4 h [3].

(See Tables 11-4 and 11-5)

Special Patient Populations [10]

- **Low-Risk PE**
  - If adequate home circumstances, patient expected to be compliant with medications, and follow up can be arranged, home treatment or early discharge should be considered [11].
  - The *Pulmonary Embolism Severity Index (PESI)* is a clinical scoring tool (see below) used to predict 30-day mortality in patients with confirmed pulmonary embolism [12]. It can help identify low-risk patients (defined by a score <85) who may be suitable for home treatment or early discharge.

TABLE 11-4

TREATMENT OF VENOUS THROMBOEMBOLISM

LOCATION	TREATMENT	COMMENTS
Provoked Proximal LEDVT, UEDVT, or PE	3 Months AC For DVT: compression stockings (20–30 mmHg) to reduce swelling	■ Proximal LEDVT: Inferior vena cava, iliac, common femoral, femoral, deep femoral, and popliteal veins ■ Proximal UEDVT: proximal to and including the axillary vein ■ Direct oral anticoagulants first line therapy for DVT/PE in non-cancer patients
Unprovoked Proximal LEDVT, UEDVT, or PE	At LEAST 3 months AC For DVT: compression stockings (20–30 mmHg) to reduce swelling	■ Low/Moderate Bleeding Risk → no stop date (periodic assessment of thrombotic versus bleeding risk is essential) ■ High Bleeding Risk → Consider stopping after 3 months ■ If stopping AC, aspirin monotherapy recommended if not otherwise contraindicated
Isolated Subsegmental PE	AC vs. Monitoring	■ High risk[a] for recurrent VTE → AC ■ Low risk for recurrent VTE → Clinical surveillance
Isolated Distal DVT (below knee)	3 Months AC vs. Monitoring	■ Distal DVT: Anterior and posterior tibial, peroneal, soleal, and gastrocnemial veins ■ AC → severe symptoms or risk factors for extension[b] ■ Monitoring → serial imaging for 2 weeks, if proximal extension of thrombus then AC 3 months ■ Distal UEDVT (brachial, radial, ulnar veins) can be managed in similar fashion
Superficial Venous Thrombosis	Symptomatic therapy ± VTE prophylaxis	■ Often affects lower limbs (saphenous and varicose veins) ■ Symptomatic therapy includes NSAIDs, warm compresses, and compression stockings ■ 45 day course of VTE prophylaxis warranted if thrombus > 5 cm or near saphenofemoral junction
Central Venous Catheter Associated UEDVT	3 months AC if axillary or more proximal involvement	■ No need to remove catheter if functional and ongoing need for its use ■ Continue AC as long as catheter remains in place and for 3 months post removal

AC anticoagulation, *DVT* deep vein thrombosis, *LEDVT* lower extremity deep vein thrombosis, *NSAID* non-steroidal anti-inflammatory drug, *PE* pulmonary embolism, *UEDVT* upper extremity deep vein thrombosis, *VTE* venous thromboembolism

[a]Active cancer, hospitalized or reduced mobility, no reversible risk factor for VTE

[b]Positive D-dimer, extensive thrombus, close to proximal veins, unprovoked, active cancer, history of VTE, inpatient status

TABLE 11-5

VENOUS THROMBOEMBOLISM—DRUGS AND DOSING

DRUG (TRADE NAME)	DOSING	CLASS	ROUTE	ROUTINE COAGULATION MONITORING	COMMENTS
Apixaban (Eliquis)	**Initial**: 10 mg BID × 7 days **Maintenance**: 5 mg BID **Prophylaxis VTE Recurrence**[a]: 2.5 mg BID	Factor Xa Inhibitor	Oral	N/A[b]	■ No dosage adjustment in renal disease though patients with CrCl <25 ml/min and Cr >2.5 mg/dL excluded from trials ■ Avoid in severe liver disease ■ Reversal Agent → Andexanet alfa
Rivaroxaban (Xarelto)	**Initial**: 15 mg BID × 21 days **Maintenance**: 20 mg daily **Prophylaxis VTE Recurrence**[a]: 10 mg daily	Factor Xa Inhibitor	Oral	N/A[b]	■ Avoid if CrCl <30 mL/min ■ Avoid in severe liver disease ■ Reversal Agent → Andexanet alfa
Edoxaban (Savaysa)	**Initial**: 5–10 days parenteral[c] AC **Maintenance**: 60 mg daily	Factor Xa Inhibitor	Oral	N/A[b]	■ Weight ≤60 kg or CrCl 30–50 mL/min decrease dose to 30 mg daily ■ Avoid in severe liver disease
Dabigatran (Pradaxa)	**Initial**: 5–10 days parenteral[c] AC **Maintenance**: 150 mg BID	Direct Thrombin Inhibitor	Oral	N/A[d]	■ Avoid if CrCl <30 mL/min ■ Reversal agent → Idarucizumab (monoclonal antibody)
Warfarin (Coumadin)	**Initial**: Parenteral[c] AC for minimum of 5 days **WITH** warfarin until INR >2 for at least 24 h **Maintenance**: Variable, usually 2–10 mg daily	Vitamin K Antagonist	Oral	INR Target 2–3	■ Preferred therapy in severe renal disease, though apixaban is approved as well
Enoxaparin (Lovenox)	1 mg/kg BID or 1.5 mg/kg daily	Low Molecular Weight Heparin (LMWH)	SQ	N/A[e]	■ First line therapy in patients with cancer and pregnancy ■ Preferred therapy in liver disease and coagulopathies ■ CrCl <30 mL/min reduce dose to 1 mg/kg daily

TABLE 11-5

(CONTINUED)

DRUG (TRADE NAME)	DOSING	CLASS	ROUTE	ROUTINE COAGULATION MONITORING	COMMENTS
Unfractionated Heparin	**Initial**: IV bolus 80 units/kg **Maintenance**: 18 units/kg/h (alternative regimens available)	Heparin	IV	aPTT Target institution (reagent) specific	■ Adverse Reaction: Heparin induced thrombocytopenia (also seen with LMWH though less frequently)

AC anticoagulation, *aPTT* activated partial thromboplastin time, *BID* twice a day, *CrCl* creatinine clearance, *INR* international normalized ratio

[a]Must have completed ≥6 months therapeutic anticoagulation with no indication to continue full dose therapy [8, 9]

[b]Anti-factor Xa activity can be measured and is the preferred test to rule out clinically significant serum concentrations

[c]Parenteral agents include unfractionated heparin, enoxaparin, fondaparinux, argatroban, and bivalirudin

[d]Thrombin time can be measured and is the preferred test to rule out clinically significant serum concentrations

[e]Monitoring anti-factor Xa levels is recommended in pregnancy and has been used in patients with obesity and renal failure

- 1 point for each year of age
- 10 points for male sex
- 20 points for a heart rate ≥110 beats/min
- 30 points for cancer
- 10 points for heart failure
- 10 points for chronic lung disease
- 30 points for a systolic pressure <100 mmHg
- 20 points for a respiratory rate >30 times/min
- 20 points for a body temperature <36 °C
- 60 points for an altered mental state
- 20 points for an arterial oxygen saturation value <90%

■ **Recurrent VTE on Anticoagulant Therapy**

– If recurrence occurs on VKA or OAC therapy, switch to LMWH [11].
– If recurrence occurs on LMWH, increase dose by 1/4 to 1/3 [11].

Intervention for DVT

■ **Catheter Directed Therapy (CDT)**

– Not recommended routinely over anticoagulation for proximal DVT [11].
– Indicated in patients with venous ischemia (i.e. phlegmasia).
– May reduce moderate-severe post-thrombotic syndrome if performed in ilio-femoral DVT.
– Benefit versus harm should take into account:

1. symptom duration (i.e. less than <14 days more likely to benefit)
2. functional status
3. life expectancy
4. bleeding risk

– Common regimen → alteplase 1mg/hour infusion for 12–24 h.
– Systemic thrombolysis and operative venous thrombectomy alternative treatments though catheter directed therapy is the preferred method in these select populations.
– Anticoagulation intensity and duration after CDT is the same as in those who did not receive thrombosis removal.

Role of IVC Filter

- VTE with contraindication to anticoagulation (i.e. actively bleeding)
- Recurrent VTE despite adequate anticoagulation
- There are moderate quality data to support IVC filters as an adjunct to therapy in patients with PE who are hemodynamically unstable [13].
- **NOT** recommended as an additive therapy in patients with acute DVT or PE treated with anticoagulation.
- Note that IVC filters do not eliminate the risk of PE and INCREASE the risk of DVT.
- If IVC filter is inserted it should be retrieved promptly after anticoagulation has been tolerated or after the indication has passed.

Submassive PE

- Anticoagulation first line therapy
  - Select patients with clinical deterioration and low bleeding risk may benefit from catheter directed thrombolysis.
    - Decreasing systolic BP but above 90 mmHg
    - Worsening hypoxia
    - Signs of right ventricular dysfunction
    - Increasing levels of cardiac biomarkers
- Admission to a telemetry unit for closer monitoring of patient status. Early recognition of clinical deterioration can be lifesaving. These patients may sometimes require intensive care unit (ICU) level of care.

Massive PE

- **Thrombolytic Therapy**
  - Peripheral IV systemic therapy first line treatment [11].
  - Delivery through peripheral vein allows for quick and easy administration.
  - Some publications exist on the merits of "half-dose" systemic lysis. These have not risen to consensus.
- **Interventional Catheter Directed Therapy**
  - Delivers thrombolytic therapy directly into the pulmonary arteries achieving high local concentrations at ≈1/4 systemic dose.
  - Thrombus fragmentation and aspiration can be used in conjunction with thrombolytic therapy or even without (high bleeding risk).
  - Recommended for those who failed systemic thrombolysis, have a high bleeding risk, or develop shock likely to cause death before systemic thrombolysis can take effect.
- **Surgical Embolectomy**
  - Reserved for patients with contraindication to thrombolysis or failed thrombolysis, or to those who develop shock that is likely to cause death before thrombolysis can take effect.
  - Patients with right atrial/ventricular thrombus, paradoxical embolism with evidence of an intracardiac shunt (i.e. patent foramen ovale) are more likely to benefit from surgery.
- **Extracorporeal Membrane Oxygenation (ECMO)**
  - May be used either as a bridge to intervention in unstable patients or in patients with contraindication to thrombolysis or failed thrombolysis to improve oxygenation and hemodynamic stability.
- **Intensive Care Unit (ICU) Care**
  - ICU care essential component to treatment and recovery as patients often on mechanical ventilation, vasopressors, inotropic agents, or ECMO. Close monitoring for bleeding post thrombolysis is also critical.

■ **Examples of Contraindications to Thrombolysis**

- Active internal bleeding or severe coagulopathy
- Cerebrovascular event, neurosurgical procedure, cerebral trauma in the past 3 months
- History of hemorrhagic stroke
- Active intracranial malignancy
- Aortic dissection
- Intracranial vascular malformation

COMPLICATIONS OF VTE

■ **Post-thrombotic syndrome (PTS)**

- Chronic lower extremity swelling, pain, discomfort with walking. skin discoloration (stasis dermatitis), venous ulcers.
- Occurs in around 1/3 of patients after acute DVT.
- Increased risk with proximal iliofemoral DVT (published rates ≈60%).

Prevention:

- ■ Consider early catheter-directed lysis for newly diagnosed iliofemoral DVT, followed by venoplasty/stenting of proximal occluded deep veins [14].
- ■ Graduated compression stockings no longer recommended for use in prevention of PTS, though these are still considered useful for symptom control.
- ■ Early ambulation over initial bed rest.

Treatment:

- ■ Once PTS develops, treatment options are frustratingly scarce.
- ■ Compression therapy (stockings and/or intermittent compression device).
- ■ Skin care and wound care when relevant.

■ **Phlegmasia (Massive Iliofemoral Thrombosis)**

- Presents as pain, swelling, cyanosis, and gangrene of the affected limb.
- *Phlegmasia alba dolens "White Leg"* → patent collaterals, no cyanosis, early signs of arterial compromise.
- *Phlegmasia cerulea dolens "Blue Leg"* → obstructed collaterals with resultant compartment syndrome, arterial compromise, cyanosis, and venous gangrene.
- Malignancy most common risk factor, seen in 20–40% of cases [15].
- Delays in therapy associated with high rates of limb loss and mortality.
- Treatment includes immediate anticoagulation and limb elevation with likely catheter-directed thrombolysis. Open surgical thrombectomy alternative therapy for those who cannot undergo thrombolysis or when a mechanical cause is suspected. Fasciotomies are sometimes required.

Complications of PE

■ **Chronic Thromboembolic Pulmonary Hypertension**

- Rare complication seen in ~3% of patients treated for PE [3].
- Fibrotic thrombi in the pulmonary arteries leads to obstruction and resultant pulmonary hypertension.
- Difficult to diagnose early in course as symptoms often non-specific. Advanced disease defined by right sided heart failure.
- Diagnosis → V/Q scan combined with single-photon emission CT imaging.
- Medical treatment includes lifelong anticoagulation.
- Surgical therapy with pulmonary thromboendarterectomy is the current standard therapy. It is recommended if performed by an experienced team and post-surgical ICU care is essential for excellent results.
- Balloon angioplasty is emerging as a valid alternative to surgery in expert centers.

REVIEW QUESTION

An 80 year-old male presents to his primary care physician's office with a complaint of worsening shortness of breath for the last 2 days. He has also noticed that his left leg has been "swelling up" over the past week and is associated with mild discomfort.

He has a past medical history of hypertension, coronary artery disease, hyperlipidemia, and prostate cancer diagnosed 3 years ago status post surgical resection and radiation therapy. He has been in remission for two years. He had a right hip replacement one month ago due to a fall and resultant hip fracture. His medications include aspirin 81 mg, metoprolol 25 mg BID, metformin 500 mg BID, lisinopril 40 mg, and atorvastatin 40 mg.

Due to concern for possible DVT/PE his doctor sent him to the emergency department for evaluation. His vital signs are within normal limits and his labs are significant only for a mild leukocytosis. Troponin and BNP are within normal limits. Due to high suspicion for PE he is sent for a CTPA which reveals an acute PE involving the left main, lobar, and segmental pulmonary artery without evidence of right heart strain. The patient is started on anticoagulation and admitted to the hospital. The following day a venous duplex ultrasound confirms an acute left common femoral DVT. He has a transthoracic echocardiogram which reveals normal left and right ventricular function, no significant valvular disease, and no pulmonary hypertension.

Which of the following statements is **TRUE**?

(a) Given history of cancer treatment duration should continue indefinitely
(b) Eliquis 5 mg BID is an appropriate regimen for anticoagulation going forward
(c) Given history of cancer lovenox is first line therapy
(d) Early ambulation over bed rest has been shown to reduce the risk of developing PTS
(e) IVC filter is an appropriate consideration in this patient to prevent further clot migration

Answer D: PTS is a frequent complication of DVT that can be associated with significant morbidity. Early ambulation over bed rest has been shown to reduce the risk of developing PTS. Compression stockings are no longer recommended for routine use but can be helpful for symptom control. Consideration should also be given to catheter directed thrombolysis in select patients [14].

This patient developed a provoked DVT/PE one month after hip replacement surgery. Under these circumstances three months of anticoagulation would be appropriate. He has a history of cancer however this is not a reason for indefinite anticoagulation. Low molecular weight heparin (i.e. lovenox) is the first line therapy in patients with active cancer. Our patient though has been in remission for two years with no signs of active malignancy. He should however undergo reevaluation for a recurrence of malignancy given his history. Eliquis is an appropriate choice of drug in this patient, however the first seven days of treatment are at a higher dose of 10mg BID. This is followed by 5 mg BID for the duration of therapy. IVC filter placement is not indicated in our patient with stable PE with no contraindication to anticoagulation. It may play a role as an adjunct to anticoagulation in patients with massive PE who cannot undergo thrombolysis or surgical embolectomy, however data is limited [13].

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CHAPTER 12

ANNE M. VAN BEUNINGEN AND GREGORY D. LEWIS

Pulmonary Hypertension

CHAPTER OUTLINE

INTRODUCTION

The right ventricular-pulmonary vascular unit is a low resistance, high compliance system that is normally capable of accommodating large increases in blood flow with a minimal increment in pressure. The development of chronically elevated pulmonary arterial pressures, either in unselected populations or in individuals with a variety of cardiopulmonary diseases, is increasingly recognized to be associated with a markedly increased risk of mortality. Regardless of the etiology, pulmonary hypertension leads to right ventricular dysfunction that is closely associated with impaired exercise capacity, renal and hepatic dysfunction. This chapter will briefly review the epidemiology and pathophysiology of pulmonary hypertension (PH) in addition to current diagnostic and treatment approaches with particular emphasis on PH arising in the setting of other cardiovascular diseases.

OVERVIEW

A) **Pulmonary Hypertension (PH)**

- Definition: An abnormally high blood pressure within the arteries of the lungs
- Hemodynamic diagnostic criteria
  - Mean pulmonary artery pressure (mPAP) > 20 mmHg at rest measured by right heart catheterization.
- Can be further characterized into one of three hemodynamic profiles based on mPAP and pulmonary capillary wedge pressure (PCWP)
  - Pre-capillary PH (mPAP >20 mmHg, PCWP ≤15 mmHg and PVR ≥3 WU)
    - Includes patients with WHO Groups 1, 3, 4 and 5
  - Post-capillary PH (mPAP >20 mmHg, PCWP >15 mmHg and PVR <3 WU)
    - Includes patients with WHO Groups 2 and 5
  - Combined pre- and post-capillary PH (mPAP >20 mmHg, PCWP >15 mmHg and PVR ≥3WU)
    - Includes patients with WHO Groups 2 and 5

B) **Pulmonary arterial hypertension (PAH)**

- Definition: A syndrome caused from restricted blood flow through the pulmonary circulation leading to elevation in pulmonary resistance and subsequent right heart failure in the absence of other causes of pre-capillary PH including primary lung disease and chronic thromboembolic disease. Hemodynamic characteristics include:
  - Mean pulmonary artery pressure (PAP) >20 mmHg and
  - Pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and
  - Pulmonary vascular resistance (PVR) >3 Woods units

C) **Pathology**

- Elevated PVR due to
  - Loss of vascular luminal cross sectional area due to vascular remodeling from excessive cell proliferation and decreased rates of apoptosis
  - Impaired endothelial function with excessive vasoconstriction (low nitric oxide and prostaglandin bioavailability, increased thromboxane A2)
  - Thrombosis in situ (platelets depleted of serotonin)
  - Smooth muscle cell proliferation
- 2 hit hypothesis
  - Permissive genotype (i.e. Bone Morphogenic Protein [BMP] 2 mutation)
  - Second insult (i.e. thromboembolism, toxin, infection)
- Histology
  - Predominantly small pulmonary arteries
  - Intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, inflammation
- Genetics
  - 10% of cases are familial
  - Most common mutation is in *BMPR2* (75%), other known mutations include *BMPR1, SMAD9*, activin receptor-like kinase1 and endoglin

D) **World Health Organization (WHO) Group Classifications** (Table 12-1)

TABLE 12-1

WHO GROUP CLASSIFICATION OF PULMONARY HYPERTENSION

WHO GROUP 1 PULMONARY ARTERIAL HYPERTENSION	WHO GROUP 2 PH DUE TO LEFT HEART DISEASE	WHO GROUP 3 PH ASSOCIATED WITH LUNG DISEASE AND/OR HYPOXEMIA	WHO GROUP 4 PH DUE TO CHRONIC THROMBOTIC AND/OR EMBOLIC DISEASE (CTEPH)	WHO GROUP 5 PH WITH UNCLEAR MULTIFACTORIAL MECHANISMS
■ Idiopathic PAH ■ Heritable PAH: BMP2R, ALK-1, ENG, ENG, SMAD9, CAV1, KCNK3 ■ Drug and toxin induced ■ Associated with: Connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis ■ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis ■ Persistent pulmonary hypertension of the newborn	■ Left ventricular systolic dysfunction ■ Left ventricular diastolic dysfunction (HFpEF) ■ Valvular disease ■ Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	■ Chronic obstructive lung disease ■ Interstitial lung disease ■ Other pulmonary diseases with mixed restrictive and obstructive pattern ■ Sleep-disordered breathing ■ Alveolar hypoventilation disorders ■ Chronic exposure to high altitude ■ Developmental abnormalities		■ Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders, splenectomy ■ Systemic disorders: Sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis ■ Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders ■ Others: Tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

DIAGNOSTIC WORK UP

A) **History**

- Symptoms: Dyspnea on exertion, fatigue, chest pain, syncope, palpitations, lower extremity edema
- WHO functional classification for patients with diagnosed pulmonary hypertension:
  - Class I: No limitations in physical activity
  - Class II: Slight limitation in physical activity, comfortable at rest. Ordinary physical activity results in fatigue, dyspnea, chest pain or syncope
  - Class III: Marked limitation in physical activity, comfortable at rest. Less than ordinary physical activity causes fatigue, dyspnea, chest pain or syncope.
  - Class IV: Unable to carry on any physical activity without symptoms. May have signs of right heart failure. Dyspnea and/or fatigue may be present at rest.

Table 12-2

B) **Physical Exam**

Table 12-3

TABLE 12-2

MEDICAL HISTORY ASSOCIATED WITH PULMONARY HYPERTENSION

GROUP I–PULMONARY ARTERIAL HYPERTENSION	GROUP II–PH WITH LEFT HEART INVOLVEMENT	GROUP III–PH ASSOCIATED WITH LUNG DISEASE AND/OR HYPOXIA	GROUP IV–PH ASSOCIATED WITH TO CHRONIC THROMBOTIC AND/OR EMBOLIC DISEASE	GROUP V–MISCELLANEOUS
Hemoglobinopathies ■ Sickle cell ■ β-thalessemia $^{+/+}$ ■ Hereditary spherocytosis Family history of PAH (BMPR2 mutation) Connective tissue disease ■ Limited cutaneous form of systemic sclerosis ■ SLE ■ MCTD ■ RA Liver disease/cirrhosis HIV Congenital heart disease with systemic shunt Drugs/toxin ■ Fenfluramine ■ Rapeseed oil ■ Methamphetamine ■ Cocaine Other ■ Hereditary hemorrhagic telangiectasia ■ Glycogen storage disease ■ Gaucher disease ■ Thyroid disorders ■ Splenectomy	Atrial or ventricular disease ■ Systolic heart failure ■ Heart failure with preserved EF ■ Constrictive or restrictive disease ■ Dilated cardiomyopathy Valvular disease ■ Mitral regurgitation ■ Mitral stenosis	COPD Interstitial lung disease Obstructive sleep apnea	Pulmonary embolism	Sarcoidosis Histiocytosis X Lymphangiomatosis Compression of pulmonary vessels ■ Adenopathy ■ Tumor ■ Fibrosing mediastinitis

TABLE 12-3

SIGNS OF PULMONARY HYPERTENSION [1]

EARLY PH	MODERATE TO SEVERE PH	ADVANCED PH WITH RV FAILURE
Accentuated S2 (best heard at apex)	Holosystolic murmur that increases with inspiration	Right ventricular S3
Early systolic click	Increased jugular 'v' waves	Distension of jugular veins
Mid systolic ejection murmur	Pulsatile liver	Heptomegaly
Left parasternal lift	Diastolic murmur	Peripheral edema
Right ventricular S4	Hepatojugular reflux	Ascites
Increased jugular 'a' wave		Hypotension, decreased pulse pressure, cool extremities

TABLE 12-4

ECHOCARDIOGRAPHIC PROBABILITY OF PH [2]

PEAK TRICUSPID REGURGITATION VELOCITY (M/S)	PRESENCE OF OTHER ECHOCARDIOGRAPHIC PH SIGNS	ECHOCARDIOGRAPHIC PROBABILITY OF PH
<2.8	No	Low
<2.8	Yes	Intermediate
2.9–3.4	No	Intermediate
2.9–3.4	Yes	High
>3.4	Not required	High

C) **Diagnostic Studies**

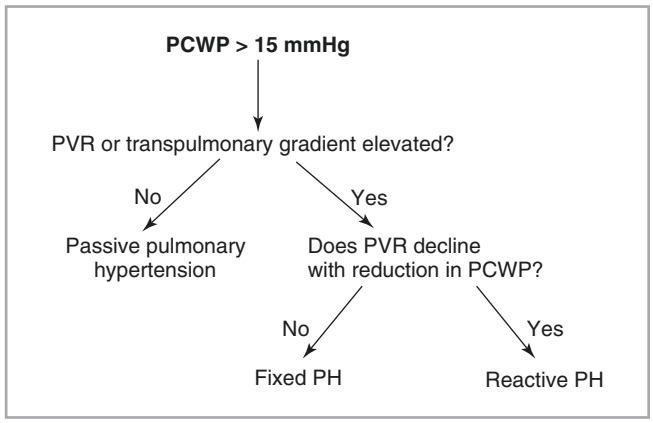
- CXR
  - Right ventricular (RV) enlargement, peripheral hypovascularity, hilar enlargement
- ECG
  - Right ventricular hypertrophy, right atrial enlargement, right axis deviation, p-pulmonale
- Trans-thoracic echocardiography
  - Echocardiographic signs can be used in addition to the peak tricuspid regurgitant velocity to assess the probability of PH (Table 12-4)
    - RV/LV basal diameter ratio >1.0
    - Flattening of the interventricular septum
    - RV outflow Doppler acceleration time <105 ms
    - Early diastolic pulmonary regurgitation velocity >2.2 m/s
    - PA diameter >25 mm
    - Inferior vena cava diameter >21 mm with decreased inspiratory collapse
    - Right atrial area >18 cm^2
  - Should always be performed when PH is suspected, and may be used to infer a diagnosis when multiple different echocardiographic measurements are consistent with PH.
  - Insufficient to support treatment decision making, cardiac catheterization required when treatment of PH is being considered.
- Further testing for diseases associated with pulmonary hypertension
  - ANA and other connective tissue disease serologies
  - Sleep study
  - Liver function tests
  - Pulmonary function tests
  - V/Q scan
  - HIV

D) **Right heart catheterization**

- Assess pulmonary vascular resistance, transpulmonary gradient (TPG, mPAP—PCWP) and diastolic pulmonary gradient (pulmonary arterial diastolic pressure—PCWP) to isolate pre-capillary and post-capillary contributions to pulmonary artery pressure (Fig. 12-1)

FIGURE 12-1

Diagnosing pulmonary venous/passive/post-capillary hypertension vs. pulmonary arterial/pre-capillary hypertension [3]



- Indicated to confirm the diagnosis of Groups 1 and 4 PH, and can be considered in Groups 2, 3 and 5 to assist in the differential diagnosis and to support treatment decisions [2]
- Pre-capillary PH
  - mPAP >20 mmHg
  - PCWP ≤15 mmHg or TPG >12 mmHg
  - PVR ≥ 3 Woods units
- **Isolated Post-capillary PH (Ipc-PH)**
  - mPAP >20 mmHg
  - PCWP >15 mmHg or TPG <12 mmHg
  - PVR <3 Woods Unit
- **Combined pre- and post-capillary pulmonary hypertension**
  - mPAP >20 mmHg
  - PCWP >15 mmHg or TPG <12 mmHg
  - PVR ≥3 Woods Units and/or DPG ≥7)
- PH can be due to high pulmonary flow in the setting of high cardiac output
- Assess for significant intra-cardiac shunt (O_2 saturations from the superior vena cava, right ventricle, pulmonary artery, and femoral artery)
- Assess for low cardiac output (cardiac index <2.1 L/min/m^2)
- Assess for vasoreactivity to pulmonary vasodilators in patients with idiopathic, heritable or drug-associated PAH (Table 12-5)
- Criteria for positive response
  - ↓mPAP by ≥10 mmHg and absolute value <40 mmHg without fall in cardiac output
  - >20% reduction in PAP and PVR with no reduction in cardiac output
  - 26.6% of 64 IPAH responders with 94% survival at 5 years compared to 55% survival of non-responders [4]
  - 12.6% of 557 IPAH patients responded to vasodilator [5]
  - 95% survival at 5 years (responders) vs. 48% (non-responders)

TABLE 12-5

AGENTS FOR ACUTE VASODILATOR TESTING [1]

	NITRIC OXIDE	ADENOSINE	EPOPROSTENOL
Route of administration	Inhaled	IV infusion	IV infusion
Dose titration	None	50 mcg/kg/min every 2 min	2 ng/kg/min every 10–15 min
Dose range	20–40 ppm for 5 min	50–250 mcg/kg/min	2–10 ng/kg/min
Side effects	↑ Left heart filling pressures	Dyspnea, chest pain, AV block	Headache, nausea, lightheadedness

TABLE 12-6

RISK STRATIFICATION OF WHO GROUP 1 PULMONARY HYPERTENSION [2]

DETERMINANTS OF RISK	LOW RISK	HIGH RISK
Clinical signs of right heart failure	Absent	Present
Progression of symptoms	No	Rapid
Syncope	No	Repeated
WHO functional class	I, II	IV
6MWD	>440 m	<165 m
Cardiopulmonary exercise testing	Peak VO2 >15 mL/min/kg VE/VCO2 slope <36	Peak VO2 <11 mL/min/kg VE/VCO2 slope >45
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 mg/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging	RA area <18 cm^2 No pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mmHg CI >2.5 L/min/m^2 SvO2 >65%	RAP >14 mmHg CI <2.0 L/min/m^2 SvO2 <60%

GROUP 1: PULMONARY ARTERIAL HYPERTENSION

A) **Epidemiology, Natural Survival, and Prognosis**

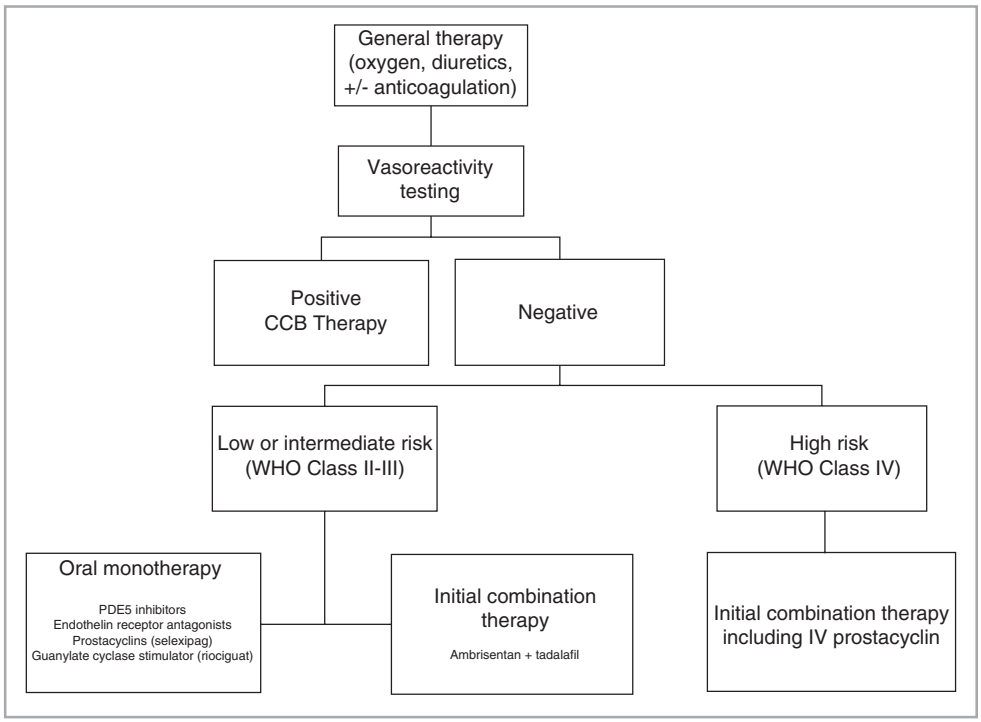
- ~15 cases/1,000,000 people [6]
  - Idiopathic PAH: ~5 cases/1,000,000 people
  - Familial PAH: ~1–2 cases/1,000,000 people
  - Associated with PAH: 8–9 cases/1,000,000 people
  - Risk Stratification of WHO Group 1 PAH is shown in Table 12-6
  - REVEAL registry data reports survival rates from the time of right heart catheterization of 85% at 1 year, 68% at 3 years, 57% at 5 years and 49% at 7 years [7]

B) **Treatment** (Fig. 12-2)

- General recommendations
  - Low level graded aerobic exercise
  - High altitudes may not be tolerated (If O_2 sat <92%, then supplemental O_2 on airplanes)
  - Avoid pregnancy (30–50% mortality rate)
- Anticoagulation in the absence of additional risk factors for thromboembolism remains controversial
  - Systematic review of seven observational studies that evaluated the effect of warfarin in patients with PAH: five studies found mortality benefit, two did not [8]

FIGURE 12-2

Treatment algorithm for Group 1 PAH [1]



- In the COMPERA registry, anticoagulation was associated with an improved 3-year survival in patients with idiopathic PAH compared with those who had other forms of PAH [9]
- The REVEAL registry did not show any survival advantage in PAH patients taking warfarin compared to matched controls [10]

- Oxygen therapy if $PaO_2 \leq 55$ mHg or $SaO_2 \leq 90\%$ at rest
- Diuretics for RV volume overload
- Calcium channel blockers (long-acting nifedipine, amlodipine or diltiazem) for patients with a positive vasoreactivity test.
  - If no improvement to NYHA Class I or II, then not a chronic responder and alternative therapy should be started.
- ±Digoxin
- Prostacyclins (Table 12-7)
- Endothelin Receptor Antagonists (Table 12-8)
- Phosphodiesterase Type 5 Inhibitors (Table 12-9)
- Surgical and endovascular interventions
  - Pulmonary artery denervation (PADN): In phase II trial of 66 patients with PAH of different causes, PADN was associated with significant improvements in hemodynamic function, exercise capacity, and cardiac function with less frequent PAH-related events and death [30]
  - Atrial septostomy: 15% mortality, improvement in 6 MW, NYHA functional class, and 30–40% bridge to transplant. Consider only for severe PAH and intractable RV failure despite maximal therapy. Goals are palliation and bridge to transplant.
  - Heart/Lung or bilateral lung transplant: the vast majority of the time lung transplant only is appropriate as RV function improves with lung transplantation. Lung transplantation is associated with increased operative mortality, but 3, 5, and 10-year outcomes similar for other indications. Consider referral for transplant evaluation in the following patients [31]:

TABLE 12-7

PROSTACYCLINS—VASODILATION WITH ANTI-PROLIFERATIVE EFFECTS

NAME	MODE OF DELIVERY	POPULATION	ADVANTAGES	DISADVANTAGES
Epoprostenol (Flolan)	IV or inhaled	■ Studied in wide range of patients with Group I PAH with class III–IV symptoms, data showing improvements in hemodynamics, functional capacity and mortality are most robust for patients with IPAH	■ Improves hemodyanamics, functional capacity and symptoms in IPAH and scleroderma-associated PAH ■ Only treatment shown to reduce mortality in IPAH in a single RCT [11]	■ Side effects—Headache, jaw pain, flushing, nausea, diarrhea, skin rash, and muscle cramping ■ Abrupt infusion cessation can lead to symptomatic deterioration and death ■ Chronic use can result in high output heart failure
Treprostinil (Remodulin, Tyvaso, Orenitram)	Remodulin: IV or subcutaneous Tycaso: Inhaled Orenitram: Oral	■ Studied in IPAH, connective tissue, and CHD related PAH patients with Class II–IV symptoms	■ Improves exercise capacity, hemodynamics and symptoms [12] ■ Oral treprostinil improves 6-min walk distance when used as monotherapy (Jing)	■ 85% of patients get pain and erythema at site of subcutaneous infusion ■ Significant and frequent side effects with oral formulation limit can dose titration ■ Transition from parenteral to oral formulation requires careful supervision
Iloprost (Ventavis)	IV, inhaled	■ Studied in Group I PAH and Group IV CTEPH patients with Class III–IV symptoms	■ Increased exercise capacity and improved symptoms, PVR and clinical events with repetitive daily inhalation compared to placebo [13]	■ Inhaled formulation requires frequent dosing (6–9 times per day) ■ Flushing and jaw pain most frequent side effects
Selexipag (Uptravi)	Oral	■ Studied in Group I PAH patients with class II–III symptoms	■ Reduced PVR after 17 weeks of therapy in pilot RCT [14] ■ Reduced composite morbidity and mortality endpoint by 40% in event-driven phase 3 RCT [15]	■ Side effects reported in up to two-thirds of patients

- ■ WHO functional class III or IV despite escalating therapy
- ■ Rapidly progressive disease
- ■ Use of parenteral targeted PAH therapy
- ■ Known or suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

■ Combination therapy

- – May be administered as two agents initiated together or as step-wise therapy
- – Tadalafil plus ambrisentan is the regimen associated with the best efficacy in PAH patients with class II or III symptoms [32]

TABLE 12-8

ENDOTHELIN RECEPTOR ANTAGONISTS—PROMOTES VASODILATION AND DECREASES SMOOTH MUSCLE PROLIFERATION

NAME	MODE OF DELIVERY	POPULATION	ADVANTAGES	DISADVANTAGES
Bosentan (Tracleer)	Oral	■ Studied in IPAH, connective-tissue disease associated PAH and Eisenmenger syndrome	■ Six RCTs have shown improvements in exercise and functional capacity, hemodynamics, echocardiographic variables and time to clinical worsening [16–20]	■ **Black Box Warning**: Dose dependent abnormal hepatic function—Check LFTS monthly ■ Teratogenic: Barrier techniques recommended as hormonal methods may be less effective ■ May cause testicular cancer and male infertility ■ Syncope, flushing, anemia, and erythema
Ambrisentan (Letairis)	Oral	■ Studied in IPAH, and PAH associated with connective tissue disease and HIV infection with class II-IV symptoms	■ Two large RCTs have shown improvements in symptoms, exercise capacity, hemodynamics and time to clinical worsening [21] ■ Monthly LFT monitoring not mandated in USA	■ Incidence of abnormal LFTs ranges from 0.8 to 3% Peripheral edema is a frequent side effect
Macitentan (Opsumit)	Oral	■ Studied in IPAH, HPAH, and PAH related to connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV and drug/toxin exposure	■ Shown to increase exercise capacity and reduce time from initiation of treatment to composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with IV or C prostanoids or worsening of PAH in one RCT [22] ■ No known liver toxicity	■ Can cause significant anemia

GROUP II: PULMONARY HYPERTENSION DUE TO LEFT HEART DISEASE

A) **Overview**

- Incidence greatly exceeds the population with Group 1 pulmonary hypertension (Fig. 12-3).
- Even with optimization of underlying etiology of elevated PA pressures, there will be a population who have PA pressures "out of proportion" to the expected pulmonary vascular response (Fig. 12-4).
- Often initially presents at passive congestion with pulmonary venous hypertension with subsequent remodeling of pulmonary arteries leading to an increase in pulmonary artery resistance as a possible mechanism for preventing pulmonary edema.
- RV Dysfunction and pulmonary hypertension determines survival in patients with moderate systolic and diastolic heart failure
  - 20% survival at 5 years with RV Ejection Fraction (RVEF) <35% and high PA pressures vs. 80% survival with normal RVEF and PA pressures. [34]

TABLE 12-9

PHOSPHODIESTERASE 5 INHIBITORS AND GUANYLATE CYCLASE STIMULATORS—REDUCE DEGRADATION AND ENHANCE PRODUCTION OF CGMP AND POTENTIATE VASODILATORY EFFECTS OF NO

NAME	MODE OF DELIVERY	POPULATION	ADVANTAGES	DISADVANTAGES
Sildenafil (Revatio)	Oral	■ Studied in IPAH or PAH associated with connective tissue disease, or repaired congenital systemic-to-pulmonary shunts	■ Four RCTs have shown improvements in exercise capacity, symptoms and/or hemodynamics [23–26]	■ Headaches, flushing, dyspepsia, epistaxis
Tadalafi (Adcirca)	Oral	■ Studied in idiopathic/heritable or related to anorexigen use, connective tissue disease, HIV infection, or congenital systemic-to-pulmonary shunts in Class II–IV patients	■ Improved 6 MW test and prolonged time to clinical worsening [27]	■ Headaches, myalgias, flushing
Vardenafil (Staxyn)	Oral	■ Studied in IPAH, PAH associated with connective tissue disease and PAH from repaired congential systemic-to-pulmonary shunts	■ In one RCT shown to improve exercise capacity, hemodynamics and time to clinical worsening [28]	■ Headaches, myalgias, flushing
Riociguat	Oral	■ Studied in IPAH, HPAH or associated with connective-tissue disease, congenital heart disease, portal hypertension with cirrhosis or anorexigen or amphetamine use	■ Improved exercise capacity, hemodynamics, WHO-FC and time to clinical worsening [29]	■ Most common serious event is syncope ■ Contraindicated in combination with PDE-5i due to hypotension

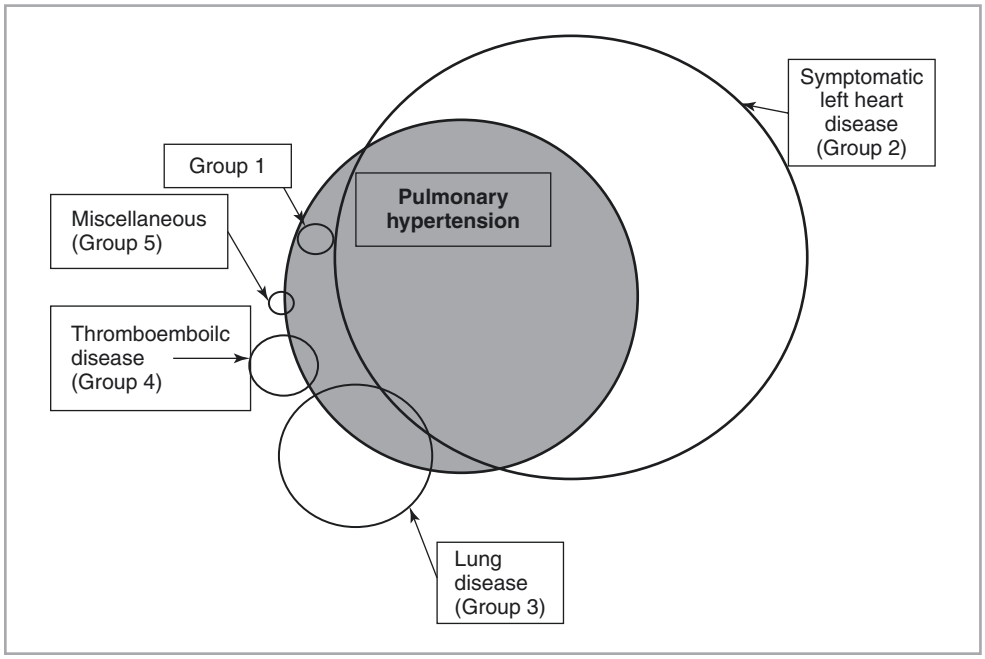


FIGURE 12-3

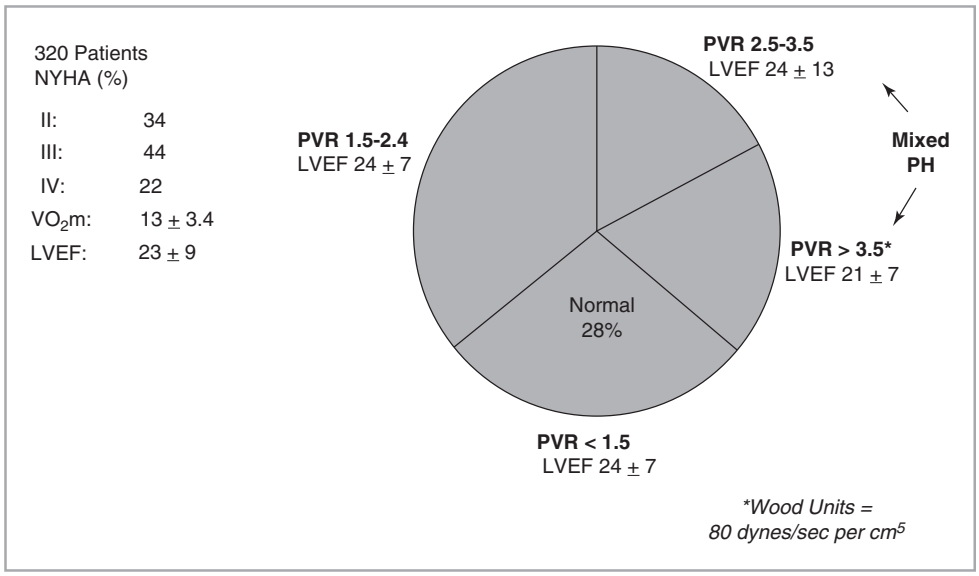
Pulmonary hypertension epidemiology synopsis

■ Pulmonary hypertension is common and predicts mortality in HFpEF [35]

- Prevalence of PH in HFpEF >80%
- Estimated 50% survival of patients with HFpEF at 3 years if PASP >48 mmHg
- Better predictor of mortality than E/e′ ratio, left atrial volume index, relative wall thickness, left ventricular mass index

FIGURE 12-4

Pulmonary hypertension out of proportion to PCWP is common in heart failure with a preserved ejection fraction (HFpEF) [33]



B) **Treatment**

- Mainstay of treatment is optimizing management of underlying left heart disease with a focus on the use of evidence-based therapies, particularly in patients with HFrEF
- There is currently insufficient evidence to recommend PAH-specific therapies for routine use in patients with group II PH
  - Epoprostenol is contraindicated based on the FIRST that study showed increased mortality in the treatment group [36]
  - Endothelin antagonist studies failed to show any improvements in outcomes and some had an increased risk of heart failure exacerbations [37]
  - PDE-5 inhibitors have been shown to improve RV function, exercise capacity and hemodynamics in small studies [38, 39], however two subsequent RCTs of sildenafil in HFpEF found no benefit [40, 41] and in a third RCT of patients with residual group II PH after successful correction of valvular heart disease outcomes were worse with sildenafil compared to placebo [42]
  - Riociguat was studied in patients with group II PH and HFrEF and found no difference in the primary end point of mPAP or exercise capacity [43]
- One prospective, randomized controlled trial comparing PADN to sildenafil plus sham PADN in patients with combined pre- and post-capillary PH due to left heart disease showed improvements in hemodynamic and clinical outcomes in the PADN group [44]

GROUP III: PULMONARY HYPERTENSION DUE TO LUNG DISEASE OR HYPOXIA

A) **Overview**

- Most common lung diseases associated with group III PH are COPD, interstitial lung disease and combined pulmonary fibrosis and emphysema [2]
- The severity of PH does not necessarily correlate with the severity of underlying lung disease, and the most common indicators for the presence of PH are a disproportionately low DLCO and a low PCO_2 [45, 46]
- In cases of severe PH (mPAP >35), other contributing factors such as left heart disease and CTEPH should be excluded

B) **Treatment**

- Supplemental oxygen is the only therapy known to have a mortality benefit in patients with group III PH and COPD, otherwise there is no evidence to support the use of PH-specific therapies for group III PH [2]
- Management therefore involves supplemental oxygen for patients who are hypoxemic and treatment of the underlying lung disease

GROUP IV: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

A) **Overview**

- Gradual formation of organized thromboemboli after deep venous thrombosis (DVT) or pulmonary embolism (PE) with distal pulmonary microvascular changes due to
  - Obstruction of small, subsegmental elastic pulmonary arteries
  - Vasculopathy of the small muscular arteries with pathology similar to IPAH [47]
- Exact incidence unknown, but thought to occur in up to 10% of patients within the first 2 years of a PE [48]

B) **Diagnosis**

- Based on findings obtained after at least 3 months of anticoagulation (to distinguish between subacute PE) and include the following [2]
  - mPAP ≥25 mmHg and PCWP ≤15 mmHg
  - Mismatched perfusion defects on V/Q scan
  - Specific diagnostic signs for CTEPH seen on CT angiography, MR imaging or pulmonary angiography (ring-like stenoses, webs/slits and chronic total occlusions)
- V/Q scanning is recommended as the first-line imaging modality for diagnosing CTEPH with a sensitivity of 96–97% and a 90–95% specificity [49]

C) **Treatment**

- Anticoagulation
  - First step in management of CTEPH
  - Lifelong anticoagulation is recommended
  - No data on the efficacy and safety of the novel anticoagulants
- Surgical treatment
  - Surgery is the only definitive therapy for CTEPH and pulmonary endarterectomy is generally the procedure of choice
  - Should be considered in all patients who have technically operable disease
  - General criteria for surgery include preoperative class II–IV symptoms and surgical accessibility of thrombi [2]
- Percutaneous treatment
  - Balloon pulmonary angioplasty (BPA) can be considered in patients with symptomatic, inoperable CTEPH or for persistent or recurrent PH following surgical treatment [50].
  - In general, lobar and proximal segmental disease is appropriate for surgical resection whereas distal segmental and subsegmental disease is better suited for BPA

- Medical therapy
  - Targeted PH therapy can be considered in addition to anticoagulation in non-operable patients although there is no evidence that supports the use of one specific medication over another
  - In patients with class II or III symptoms, oral medications including riociguat, bosentan and sildenafil may be preferred
  - In patients with class IV symptoms, IV prostanoids can be considered

QUESTIONS AND ANSWERS

1. A 45 year-old woman with mixed connective tissue disorder comes to the emergency room with 6 months of progressive lower extremity edema and dyspnea. She has not been taking any medications, and on exam her pulse is 89 and blood pressure is 106/72. Her cardiac exam is significant for a 3/6 systolic murmur, loudest at the mid-left sternal border, increases with inspiration, and does not radiate to the carotids or axilla. A pulmonary artery (PA) tap is also noted along with an RV heave. She has a large *cv* wave on jugular venous pulse (JVP) exam. When examining her abdomen, a pulsatile and enlarged liver is found. Her lungs are clear. She has 2+ bilateral, lower extremity edema.

   She is admitted to the cardiology service and undergoes a transthoracic echocardiogram (TTE). The TTE shows an LVEF of 50%, severe tricuspid regurgitation, dilated RV with septal flattening, diminished Tricuspid Annular Plane Systolic Excursion (TAPSE), and a RV systolic pressure of 73 mmHg. She then undergoes a right heart catheterization that shows a PA pressure of 78/35 mmHg (mean 49 mmHg), a PCWP of 15 mmHg, and a PVR of 8 Woods units. Her cardiac index is 1.8 L/min/m^2. Vasodilator challenge decreased her mean PA pressure by 7 mmHg. Her b-type natriuretic peptide is elevated. What is the next step in her treatment?

   A) Nifedipine 120 mg/day
   B) Perform atrial septostomy
   C) Amlodipine 10 mg/day
   D) Taladafil 40 mg/day plus ambrisentan 5 mg/day

   1. Answer: D. This patient has signs and symptoms of severe Group I pulmonary hypertension, as well as predisposition with a history of mixed connective tissue disease (Table 12-2). She was not responsive to vasodilator challenge, suggesting that calcium channel blockers would not be an effective therapy. A positive vasodilatory response is met when the mean PA pressure decreased by more than 10 mmHg AND the absolute PA pressure is less than 40 mmHg without a drop in cardiac output. In addition, she has findings of high-risk pulmonary hypertension, and PH-specific therapy should be considered.

2. A 76 year-old gentleman with COPD, a 75 pack year smoking history, longstanding severe hypertension comes in to the emergency department with increasing lower extremity edema and dyspnea for the past three days. On exam he has an elevated JVP, bilateral crackles at the lung bases, and a 2/6 soft mid-systolic murmur, and a laterally displaced PMI. His abdomen was obese with a slightly enlarged liver with hepatojugular reflux. He had 2+ bilateral lower extremity edema. He was treated with nebulizers and diuretics with minimal improvement in his symptoms. A TTE was obtained that showed an LVEF of 55%, symmetric left ventricular hypertrophy, calcified mitral annulus, but no stenosis, and mild mitral regurgitation. A right heart catheterization was obtained that showed right atrial pressure = 12, PA pressures of 56/32 (mean 40), PCWP 18, cardiac output 5.8 L/min, and PVR of 3.8 Woods units. How should this gentleman be treated?

   A) Bosentan 62.5 mg po bid
   B) Furosemide 40 mg iv bid
   C) Amlodipine 10 mg po daily
   D) Treprostinil 1.25 ng/kg/min sc continuously

   2. Answer: B. This patient has signs of mixed pulmonary hypertension from diastolic heart failure (WHO Group II) (Table 12-1). Pulmonary hypertension due to left heart failure may consist of passive pulmonary congestion, with elevated PCWP and PAP, but low PVR. Alternatively, some patients with HF present with "out of proportion" PH characterized by a PVR > 3 Woods units. In HFpEF patients, out of proportion pulmonary hypertension is common. Pulmonary vasodilator therapy has not been evaluated sufficiently in this population to recommend its usage. Optimization of volume management remains the mainstay of treatment for this condition.

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CHAPTER 13

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Vascular Disease and Venous Thromboembolism

CHAPTER OUTLINE

ABBREVIATIONS

ABI	Ankle-brachial index
ACE	Angiotensin converting enzyme
ALI	Acute limb ischemia
ARAS	Atherosclerotic renal artery stenosis
ARB	Angiotensin II receptor blocker
ASA	Aspirin
CAS	Carotid artery stenting
CCB	Calcium channel blocker
CEA	Carotid endarterectomy
CKD	Chronic kidney disease
CLI	Critical limb ischemia
CTA	Computed tomographic angiography
CV	Cardiovascular
DP	Dorsalis pedis
DM	Diabetes mellitus
DVT	Deep venous thrombosis
FMD	Fibromuscular dysplasia
HTN	Hypertension
LIMA	Left internal mammary artery
MI	Myocardial infarction
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NSTEMI	Non-ST-elevation myocardial infarction
PAD	Peripheral artery disease
PE	Pulmonary embolism
PT	Posterior tibial
RBBB	Right bundle branch block
RVSP	Right ventricular systolic pressure
TBI	Toe-brachial index

PERIPHERAL ARTERY DISEASE (PAD)

Prevalence

- ~4% in patients over age 40
  - Increases with age and cardiovascular (CV) risk factors
  - ~15–30% in patients over age 70
- CV Implications [1]
  - Roughly 50% of PAD patients will have coronary artery disease (CAD)
  - CV events are more common than ischemic limb events
  - Ankle-brachial index (ABI) < 0.7 = risk of myocardial infarction (MI) is 20% at 5 years (double the highest-risk Framingham group)
  - ABI 0.7–0.09 = risk of MI is 10% at 5 years
- Patients at risk for PAD (All of the below risk groups have pre-test probabilities of over 15% and should be screened for PAD):

  Table 13-1 Groups with high PAD prevalence

Presentation—Fig. 13-1

- Symptoms
  - Typical claudication—cramping calf pain exacerbated by exertion and relieved by rest; symptoms suggestive of femoral or popliteal disease
  - Atypical claudication—exertional hip, thigh or buttock pain; impotence; symptoms suggestive of aortoiliac artery disease

TABLE 13-1

GROUPS WITH HIGH PAD PREVALENCE

Known atherosclerotic coronary, carotid, or renal artery disease
Age > 70
Age > 50 with DM or smoking
Age < 50 with DM and an additional risk factor (smoking, hypertension, hyperlipidemia)
Abnormal LE pulse examination
Exertional leg symptoms

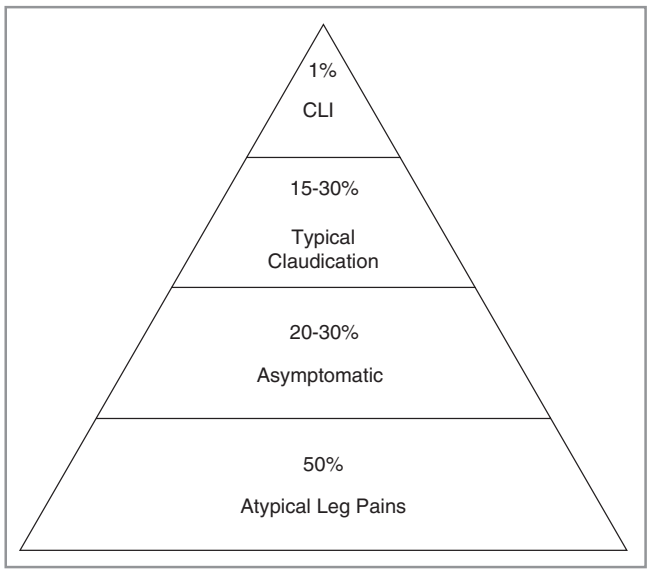

FIGURE 13-1

Presentation of PAD

- Critical limb ischemia (CLI)—pain at rest in the foot, non-healing ulcer, gangrene
- Acute limb ischemia (ALI)—sudden (<2 weeks) development of pain, pulselessness, pallor, coolness, and weakness [2]; severity classified into three categories:
  - I—Viable (not immediately threatened)
    - no muscle weakness or sensory loss; + arterial/venous doppler signals
  - II—Threatened
    - Mild-moderate weakness or sensory loss; absent arterial but + venous doppler signal
  - III—Irreversible
    - Major tissue loss or nerve damage is inevitable
    - Severe muscle loss/paralysis, severe sensory loss/anesthesia, both arterial and venous signals absent

- Physical examination
  - Poor peripheral pulses (femoral, popliteal, pedal)
  - Femoral artery bruit on auscultation
  - Elevation pallor (foot develops pallor when raised)
  - Dependent rubor (foot slowly becomes red when returned to the ground)
  - Poor capillary refill (>3 s)
  - Ulcerations on the toes, intertriginous spaces, borders of the feet

Testing

$$\text{ABI} = \frac{\text{Ankle systolic blood pressure}\left(\text{highest of the DP / PT pressures}\right)}{\text{Brachial artery systolic pressure}\left(\text{highest of the right / left arm pressures}\right)}$$

- ABI Interpretation
  - 1.40: uninterpretable/incompressible
  - 1.00–1.39: normal
  - 0.91–0.99: borderline
  - 0.71–0.90: mild PAD
  - 0.41–0.70: moderate PAD
  - <0.40: severe PAD
- Exercise ABI can be performed for patients with typical claudication symptoms in whom resting ABI values are normal or borderline
- Uninterpretable ABI due to incompressible vessels secondary to Mockenburg's medial artery calcification.
  - This is more common in diabetic and elderly populations.
- Toe brachial index (TBI) can be used in the setting of uninterpretable or incompressible ABI.
  - TBI <0.7 is sensitive for dx of PAD

Table 13-2 Diagnostic Tests for PAD Evaluation

TABLE 13-2

DIAGNOSTIC TESTS FOR PAD EVALUATION

	PROS	CONS
ABI	Non-invasive, fastest, office-based	No clarity regarding level of disease
Segmental pressures with pulse volume recordings	Non-invasive, rapid, no contrast	Does not clarify anatomic details
Arterial ultrasound	Non-invasive, no contrast	Operator-dependent, may not be able to image suprainguinal and/or infrapopliteal vessels, time consuming
CTA	Non-invasive	IV contrast, radiation, difficult to interpret in the setting of heavy vascular calcification
MRA	Non-invasive	Gadolinium, expensive, may overestimate stenosis severity
Digital subtraction angiography (DSA)	Best quality anatomic information, option for concurrent therapeutic procedure	Invasive, IV contrast, technical expertise necessary

Medical Management of PAD [3]

- Treat DM to glycohemoglobin <7%
- Daily Foot Care and Regular Podiatry Appointments
- Smoking Cessation
- Lipid Lowering Therapies—Statins decrease CV events and may improve leg functioning (i.e.: pain-free walking distance)
- Treatment of hypertension to guideline derived goals.
  - ACE-inhibitors may improve leg functioning
  - Beta-blockers are NOT harmful
- Anti-platelet therapy
  - Aspirin or clopidogrel should be used in all patients
    - CAPRIE trial showed a 24% decrease in CV outcomes for PAD patients treated with clopidogrel rather than aspirin [4]
    - CHARISMA study showed no decrease in CV outcomes from combining clopidogrel plus aspirin in patients with PAD [5]
    - EUCLID trial showed no significant benefit in reducing CV outcomes with the use of ticagrelor instead of clopidogrel in patients with symptomatic PAD [6]
- Coumadin—Coumadin is not recommended in addition to anti-platelet therapy for PAD [7]
  - The role of novel oral anticoagulants (NOAC) in addition to antiplatelet therapy for patients with PAD has not been well established [8]
- Symptomatic Medical Therapy
  - Supervised exercise rehabilitation improves pain-free walking distance.
  - Increased daily activity leads to decreased mortality
  - 3–6 months of cilostazol is recommended (contraindicated in patients with heart failure)

Interventional Therapy

- Contraindications
  - Lack of symptoms
  - Lack of pressure gradient across an angiographic stenosis

- Endovascular revascularization
  - Indicated if life or work-limiting symptoms exist despite the trial of medical and exercise therapy
  - Primary stenting should not be performed in the femoropopliteal segments (i.e.: use stents for failure of angioplasty or atherectomy techniques)
    - Drug-coated balloon technology appears to provide durable results for patients with femoropopliteal disease [9]
- Surgical revascularization
  - Indicated if life or work-limiting symptoms exist after a trial of medical and exercise therapy and if not a good anatomic candidate for endovascular approach
  - Autogenous vein grafts are preferred to prosthetic grafts for lower extremity bypass due to improved long-term patency
- Special topic: Critical Limb Ischemia (CLI)
  - Revascularization is indicated to provide symptom relief and promote wound healing
  - Goal is to restore "straight-line" blood flow to the foot whenever possible
    - Both the suprainguinal and infrainguinal segments may need to be treated during the same session to achieve this goal
    - "angiosome" concept describes the foot in terms of compartments that receive dedicated arterial supply
      - Wounds located within a specific angiosome are more likely to heal if arterial supply to that angiosome is restored
  - Open repair and endovascular repair of the lower extremities had equivalent results in the BASIL trial [10]
- Special topic: Acute Limb Ischemia (ALI)
  - Treatment is based on ALI category at presentation
    - Category I (not immediately threatened)
- Urgent revascularization (6–24 h) + parenteral anticoagulation
    - Category II (threatened limb)
- Emergent revascularization (within 6 h) + parenteral anticoagulation
    - Category III (irreversible)
- Primary amputation
  - Seek consultation from an expert vascular interventionalist or surgeon
  - The decision between open surgical and endovascular treatment is influenced by the likelihood of the technical success and the rapidity of revascularization with each strategy.
    - Catheter directed lysis may be preferred with recent occlusions, synthetic graft thrombosis and stent thrombosis [2]

RENOVASCULAR DISEASE

Atherosclerotic Renal Artery Stenosis (ARAS)

- Prevalence
  - Approaches 10% in consecutive patients undergoing cardiac catheterization
  - May be up to 20% in patients with a history of diabetes mellitus and hypertension
  - Risk factors for ARAS are the same as those for development of coronary artery disease

- Presentation
  - Resistant hypertension
  - Worsening renal function with addition of ACEi/ARB (most common in bilateral disease)
  - Acute pulmonary edema (in bilateral disease)
- Physical exam
  - Severe hypertension
  - Abdominal or flank bruits
  - Signs of volume overload (in bilateral disease)
- Imaging Studies
  - Doppler ultrasound—low cost, non-invasive, no iodinated contrast but sensitivity is highly operator-dependent
  - CTA—usually provides good anatomical information, requires iodinated contrast, limited in cases of heavy calcification
  - MRA—newer gadolinium-free protocols provide excellent anatomical information without risk of nephrogenic fibrosing systemic sclerosis
  - Angiography—invasive but provides best anatomic information with opportunities for true hemodynamic assessment and intervention when necessary
- Treatment
  - Aggressive medical management of hypertension with goal of normotension—often requires three or more agents
    - ACEi/ARB—first line targets RAAS pathway, but may worsen renal function in bilateral disease requiring discontinuation
      - CCB—another first line agent which is safe to use in bilateral disease
    - Thiazide/loop diuretics—second line agents to manage sodium retention
    - Beta-blockers, clonidine, vasodilators, etc. as necessary
  - Treatment of risk factors is imperative to limit disease progression and prevent adverse cardiovascular outcomes
    - Aspirin, lipid-lowering therapy, smoking cessation, diabetes control
  - Routine revascularization should not be performed for angiographically detected stenoses
  - Consider revascularization in selected clinical circumstances
    - Bilateral high-grade stenoses with heart failure out of proportion to systolic function or cardiac ischemic burden
    - High-grade stenosis with resistant hypertension (>3 maximally dosed antihypertensive meds including a diuretic)
  - Randomized trials thus far negative for benefit of stenting in ARAS but all heavily criticized
    - DRASTIC study was underpowered, angioplasty alone used, high-crossover rate, non-severe lesions treated [11]
    - STAR trial was underpowered, non-severe lesions treated, high complication rate [12]
    - ASTRAL suffered from selection bias, non-severe lesions treated, high complication rate [13]
    - CORAL trial [14]
      - Randomized 947 patients with RAS (>80% or >60% + 20 mmHg trans-lesional gradient) to PTA with stenting vs. medical therapy alone

- Primary outcome was composite of major adverse cardiac and renal events
- Major exclusion criteria: FMD, chronic kidney disease from causes other than ischemic nephropathy, serum creatinine >4 mg/dL, renal size <7 cm
- At baseline: average number of anti-HTN medications 2.1, average SBP 150 mmHg, average eGFR 58 mL/min/m^2 in both groups
- Outcome: no significant difference in clinical outcomes between the two groups at 43 months follow up
- Criticisms:
  - Trial enrolled patients with non-severe lesions, half of all patients with CKD 2 or less, BP at enrollment not markedly elevated with only two medications on board

Fibromuscular Dysplasia (FMD)

- Fibromuscular dysplasia is a syndrome caused by diffuse proliferation of vascular smooth muscle cells, leading to random stenoses in multiple vascular beds.
  - Up to 5% of all renovascular disease may be due to FMD
  - Typical patient is young and female
  - Other vascular territories may be affected (i.e.: carotid, lower extremity, mesenteric)
    - Must rule out intracerebral aneurysm
      - Present in 11.8% of all patients enrolled in the US FMD registry [15]
      - Treat with catheter-based embolization
    - Important to screen patients with FMD in one distribution for disease involvement of other vascular beds
      - Imaging modalities: CT or MR angiography
- Diagnosis
  - Doppler ultrasonography may suggest presence of stenosis, however, angiography is characteristic, with typical beads-on-a-string appearance (Fig. 13-2)
- Treatment
  - Aggressive medical treatment of hypertension often requiring multiple agents with ACEi/ARB as first-line therapy (similar to ARAS)
  - In cases of resistant hypertension, treatment with angioplasty (primary stenting is not required) can provide durable results

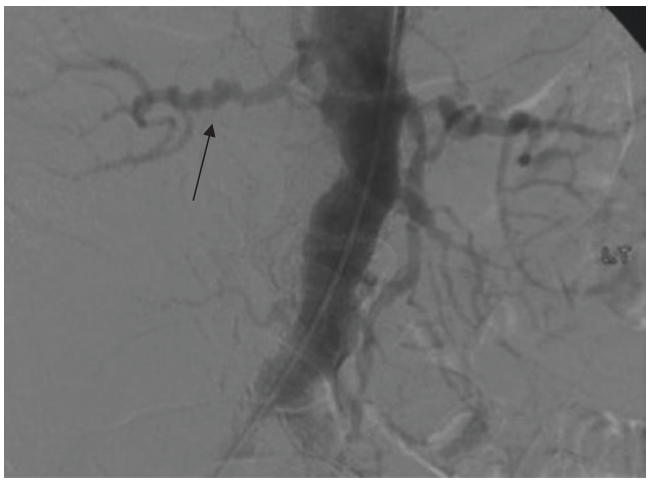

FIGURE 13-2

DSA of renal artery FMD with typical beads-on-a-string appearance (arrow) (Courtesy: Weinberg I, www.angiologist.com)

SUBCLAVIAN ARTERY DISEASE

- Symptoms
  - Most often asymptomatic
  - Arm claudication, described as fatigue > ischemic symptoms
  - Vertebral steal syndrome—developing symptoms of vertebrobasilar insufficiency with exercise using ipsilateral arm
  - Subclavian steal syndrome in patient with prior internal mammary bypass graft
    - May also lead to myocardial ischemia as a result of coronary steal
- Diagnosis
  - Arm systolic blood pressure differential greater than 15 mm Hg should raise suspicion
  - Doppler ultrasonography
  - Angiography (invasive or non-invasive)
- Treatment
  - Selected indications for revascularization
    - Vertebral steal syndrome
    - Coronary steal syndrome in a patient with a LIMA graft
    - Arm Claudication
  - Revascularization: stenting (preferred strategy) vs. carotid-subclavian bypass

CAROTID ARTERY DISEASE

- Symptomatic Disease—Transient ischemic attack or stroke within 6 months
  - Endarterectomy (CEA) or Stenting (CAS) for angiographic lesions greater than 50% or those judged to be greater than 70% on non-invasive testing
    - SAPPHIRE trial: CAS is non-inferior to CEA in symptomatic patients who are high risk for surgery [16]
  - No intervention on patients with stenoses less than 50%
  - Proceed early to revascularization (<2 weeks) after TIA/stroke
- Asymptomatic Disease
  - Controversy exists regarding medical management vs. revascularization
  - Can consider revascularization in stenoses >70% if low risk of procedure-related complications and long-term expected survival
    - Octagenerians have high procedural risk with both CEA and CAS
- CREST trial: No difference in stroke/MI/death for CAS vs. CEA in broad group of patients [17].
  - Slightly increased risk of minor stroke with CAS.
  - Slightly increased risk of NSTEMI with CEA.
- ACT-1 trial: CAS with embolic protection was non-inferior to CEA in asymptomatic patients with stenosis severity 70–99% by US or angiography [18]
  - Study employed distal embolic protection devices
  - Recent development of proximal embolic protection devices may be even more effective in procedure-related stroke prevention

- CREST-2 trial (ongoing): two parallel trials comparing revascularization strategies (surgical/endovascular) vs. contemporary medical therapy [19]
  - Carotid endarterectomy vs. medical therapy
  - Cartoid artery stenting vs. medical therapy
  - Contemporary studies evaluating management of carotid artery stenosis mostly focused on comparing surgery vs. carotid artery stenting (without inclusion of a medical therapy only arm)
    - No recent study compared revascularization to contemporary medical therapy

MESENTERIC VASCULAR DISEASE

- Prevalence
  - Angiographic stenosis may be present in over half of patients with known systemic atherosclerosis
  - Causes
    - Atherosclerosis—etiology in >90% of cases
    - Median arcuate ligament syndrome (compression of celiac artery or SMA by median arcuate ligament)
    - FMD
    - Vasculitis
  - Angiographic stenoses may not be associated with symptoms
    - Significant disease in two vessels often necessary to provoke symptoms due to rich collateral networks in the gut
  - IMA stenosis/occlusion usually well tolerated due to hypogastric, meandering mesenteric, and Marginal artery of Drummond collaterals
- Presentation
  - Symptoms of chronic mesenteric ischemia: post-prandial abdominal pain (intestinal angina), "food fear", weight loss
- Diagnosis
  - Non-invasive testing: Doppler ultrasonography, CTA, MRA
- Treatment
  - Percutaneous stenting is a viable treatment strategy in patients with atherosclerotic disease and no evidence of an arterial compression syndrome (such as median arcuate ligament syndrome)
- Acute mesenteric ischemia
  - Often due to thromboembolism or hypotension with insufficiency at watershed territories
  - Usually a surgical emergency requiring urgent laparotomy
  - Adjunctive endovascular techniques are sometimes used

DEEP VENOUS THROMBOSIS (DVT)

Incidence

- 1–2 per 1000 patient years
- Incidence increases 10-fold after age 50

Anatomy

- Proximal DVT: involving iliac, femoral, popliteal veins
- Distal DVT: involving calf veins

Risk Factors

- Malignancy
- Pregnancy
- Prior DVT
- Oral contraceptives
- May-Thurner syndrome (left common iliac vein compression by the right common iliac artery)
- Virchow's triad
  - Hypercoagulability
  - Stasis
  - Endothelial injury

Presentation

- Painful, swollen lower extremity
- Upper extremity DVT (<10% of all DVT) are usually associated with indwelling catheters or pacemaker/defibrillators

Diagnosis (Table 13-3)

Figure 13-3

Treatment

- Provoked proximal DVT: 3–6 months anti-coagulation (INR = 2–3 with warfarin)
- Unprovoked proximal DVT receives 6 months to indefinite anti-coagulation

TABLE 13-3

WELL'S SCORE FOR DVT DIAGNOSIS

CLINICAL FEATURE	SCORE
Active cancer (treatment ongoing or within 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recent bedridden for more than 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely as or greater than that of DVT	−2

Courtesy: Well et al. [20]
Interpretation: High probability >3; Moderate probability 1−2; Low probability <0

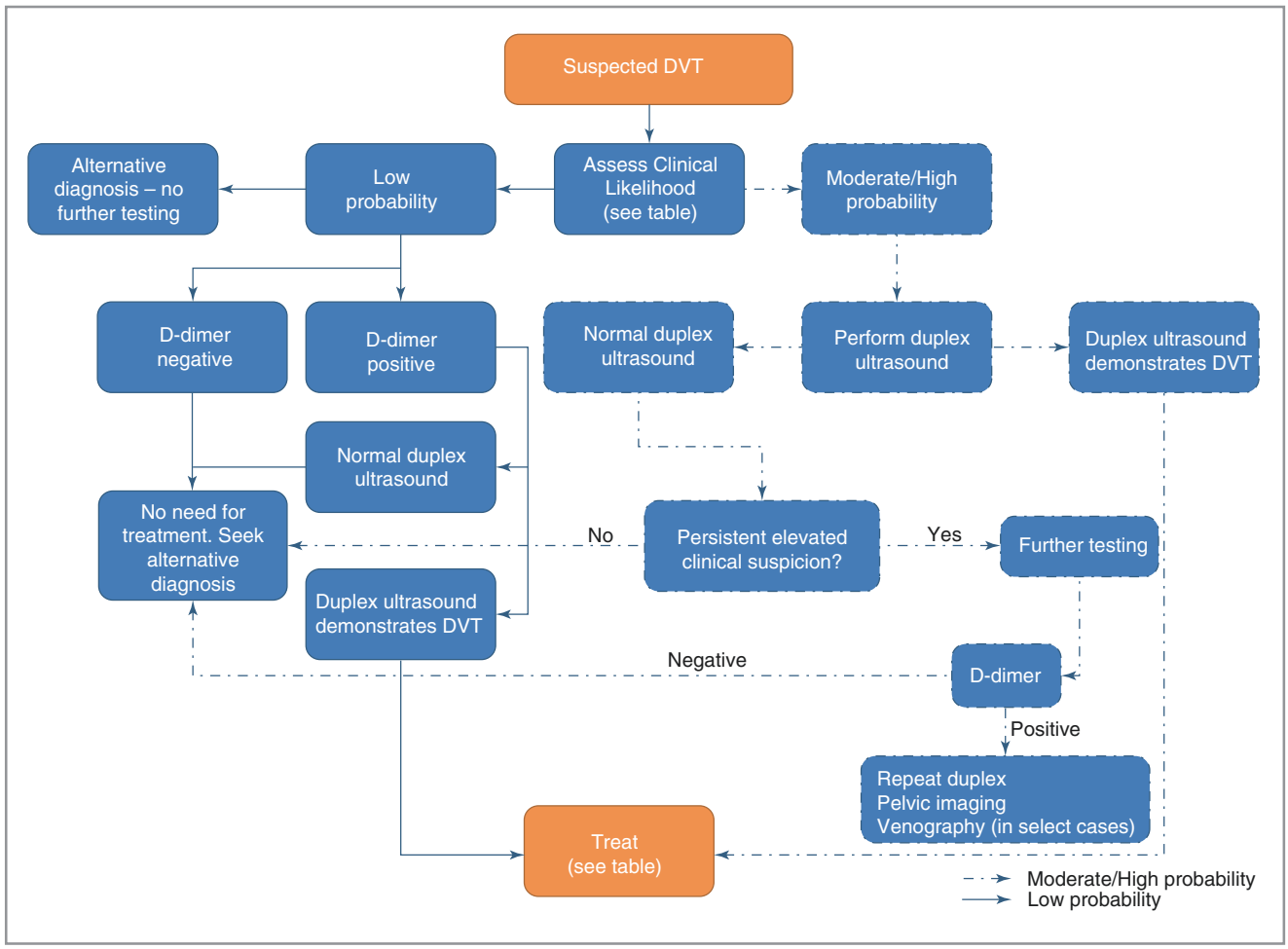

FIGURE 13-3

Diagnostic algorithm for DVT (Courtesy: Weinberg I, Jaff, M, Venous Thromboembolism, Springer's Textbook of Cardiovascular Intervention in press) [21]

  - LMWH preferred in patients with malignancy
  - Catheter-directed lysis may reduce the severity of post-thrombotic syndrome in ilio-femoral DVT [22]
  - Do not use CDT for femoropopliteal DVT

- Calf DVT: typically 3 months anti-coagulation for symptomatic pts vs. no anti-coagulation and serial ultrasonography (4–6 ultrasounds over 2–4 weeks) to monitor for proximal extension,
- Superficial venous thrombosis: non-steroidal anti-inflammatory drugs and warm compresses.
  - Consider anti-coagulation for proximal clot (i.e.: near saphenofemoral junction).
- Catheter-Associated DVT: remove catheter, anti-coagulation for 3 months or less

Complications

- Post-thrombotic syndrome (PTS)
  - Persistent long-term swelling in the lower extremity that may be associated with skin changes (stasis dermatitis)
  - Leg may feel fatigued, heavy and weak
  - Is a common consequence of proximal iliofemoral DVT
  - Prevention
  - Consider early catheter-directed lysis for newly diagnosed iliofemoral DVT
  - Use 20–40 mm Hg graduated compression stockings for long term prevention of venous insufficiency and PTS
  - Treatment
  - Compression therapy
  - Angioplasty/stenting of proximal occluded deep veins
  - Rarely open surgical bypass procedures
- Phlegmasia Dolens
  - Massive thrombosis of a limb with patent collaterals (phlegmasia alba dolens) or obstructed collaterals with resultant compartment syndrome, arterial compromise and venous gangrene (phlegmasia cerulea dolens)
  - Risk factors include post-operative states, malignancy, hypercoaguability, and May-Thurner Syndrome
  - Mortality rates are up to 25% with PE causing at least 1/3 of deaths and amputations are common
  - Presents as pain, swelling, and cyanosis of the affected limb
  - Treatment includes leg elevation, anticoagulation, catheter-directed thrombolysis, and open surgical thrombectomy

PULMONARY EMBOLISM (PE)

Incidence

- 400,000–600,000 annual causes in the US

Risk Factors Are Identical to DVT

(see section “Anatomy”)

Presentation

- Sudden onset of pleuritic chest pain
- Dyspnea
- Cough
- Hemoptysis
- Tachycardia ± hypotension

Diagnosis

- History—assess for risk factors and presenting symptoms above
- Physical exam—tachypnea, tachycardia, hypoxia, accentuated P2 component of S2, RV heave
- Electrocardiogram—sinus tachycardia, RBBB, anterior precordial repolarization abnormalities

TABLE 13-4

WELL'S SCORE FOR PE DIAGNOSIS

CLINICAL FEATURE	SCORE
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate greater than 100	1.5
Immobilization or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment, treated in the last 6 months or palliative)	1

Courtesy: Wells et al. [23]
Interpretation: High probability >6; Moderate probability >2 and <6; Low probability <2. If the D-dimer is negative a cutoff point of 4 points or less makes a PE unlikely

- D-dimer—highly sensitive but poorly specific test that is useful to rule out DVT
- Chest radiography—most commonly unremarkable, may see Westermark sign (oligemic focus distal to PE) or Hampton's hump (wedge-shaped consolidation representing infarction)
- Echocardiography—increased RVSP, right ventricular dilation and hypokinesis, interventricular septal flattening
- Well's criteria (Table 13-4)
  - For moderate or high probability proceed to CT angiogram or ventilation/perfusion (V/Q) scan

Treatment

- Immediate parenteral anticoagulation
  - Transition to long-term agents (warfarin vs. LMWH/fondaparinux)
    - Provoked PE (status post trauma, prolonged immobilization, or recent surgery) should be treated for a minimum of 3 months
    - Unprovoked PE should be treated for 6–12 months with treatment extension considered
    - Second unprovoked PE is an indication for lifelong anti-coagulation
- IVC filter for select indications
  - VTE with contraindication to anticoagulation
  - Recurrent VTE despite adequate anti-coagulation

HIGH RISK PE

- Submassive PE
  - Systolic BP ≥90 mmHg but with presence of at least one of the following:
    - RV dilation on Echocardiography (RV/LV ratio ≥1.0) [24]
    - Elevation of cardiac troponin I
    - Elevation of brain natriuretic peptide
- Massive PE
  - Systolic BP <90 mmHg
  - Need for vasopressor support

  - Cardiac arrest
    - Patients may have signs of systemic hypoperfusion (i.e. confusion, reduced urinary output, cool extremities, elevated lactic acid levels)
  - International Cooperative Pulmonary Embolism Registry showed a 4.5% incidence and greater than 50% 90-day mortality [25]
- Diagnostic studies
  - Massive PE sometimes associated with acute RV strain pattern on ECG ("S1Q3T3")
  - Transthoracic echocardiography reveals akinesia of the RV free wall with apical sparing (McConnell's sign)
- Treatment
  - Consider consulting a multidisciplinary PE response team (PERT) to discuss various treatment options [26]
  - Consider peripheral IV or catheter-directed thrombolysis
    - Absolute contraindications to thrombolysis are:
      - active internal bleeding or severe coagulopathy
      - cerebrovascular event, neurosurgical procedure, cerebral trauma in the past 3 months
      - history of hemorrhagic stroke
      - active intracranial malignancy
      - aortic dissection
    - Consider surgical or catheter-based embolectomy strategies for those not eligible for thrombolysis.
    - In cases of refractory hypotension or cardiac arrest, consider emergent mechanical circulatory support with ECMO or isolated percutaneous RVAD

QUESTIONS AND ANSWERS

1. A 44 year old woman with a history of hypertension presents to the Emergency Room with complaints of severe headaches for several days. Her outpatient medication list includes amlodipine 10 mg daily, lisinopril 40 mg daily, and hydrochlorothiazide 25 mg daily. Vital signs revealed blood pressure of 185/95 and a heart rate of 78. Examination is significant for an abdominal bruit and bilateral carotid bruits. A CT (head) does not show any signs of intracranial hemorrhage. The treatment most likely to benefit this patient is:
   a. Addition of metoprolol XL 50 mg daily to her regimen
   b. Surgical revascularization of her carotid arteries
   c. Angiography and balloon angioplasty of the renal arteries
   d. Carotid angiography with consideration of stent placement
   e. Angiography and stenting of the renal arteries

   1. Answer c. The patient's demographic information, resistant hypertension, and abdominal/carotid bruits should raise suspicion for fibromuscular dysplasia.

   Given resistant hypertension on three medications including a diuretic, renal angiography with angioplasty is indicated in this case. In FMD, stent placement is often unnecessary as good long-term results have been noted with angioplasty alone. There is no clear indication to intervene on her carotid arteries given her absence of neurologic symptoms currently. Addition of metoprolol XL to her regimen is unlikely to normalize her blood pressure.

2. A 56 year old man with a history of tobacco use, hypertension, and diabetes presents to you with complaints of right calf pain after walking two blocks. His medication regimen includes aspirin, cilostazol, ramipril, atenolol, and metformin. He has been advised to walk daily and, for 6 months, he has adhered to a regimen of 30–45 min of walking on a treadmill at his house but has to stop frequently due to right calf pain. He had a recent CTA that revealed a focal 3 cm high-grade 80% stenosis of the right external iliac artery. The next most appropriate step in management is:
   a. Addition of clopidogrel 75 mg daily to his regimen
   b. Addition of warfarin to his regimen with goal INR = 2–3.
   c. Discontinuation of atenolol.
   d. Percutaneous right external iliac artery revascularization.
   e. Continue current regimen including daily walking program with follow-up in 6 months.

   2. Answer d. The patient is on optimal medical therapy and a structured walking program. He continues to have life-limiting symptoms despite this so endovascular revascularization of

the right external iliac artery is indicated.Neither dual antiplatelet therapy nor warfarin have been shown to have benefit in this clinical circumstance. There is no need to discontinue his beta-blocker.

3. A 75 year old patient is hospitalized with a hip fracture. Their past medical history is notable for hypertension, colon cancer treated with hemi-colectomy 2 months prior to presentation, and diabetes mellitus. Their medications include metoprolol, lisinopril, metformin, and aspirin. On hospital day 2, the patient undergoes an open reduction and internal fixation of the hip, which is uneventful. On hospital day three, however, the leg contralateral to the surgical repair is edematous, painful, and indurated.

   A venous thrombosis of the proximal femoral venous system is identified using Doppler ultrasound and systemic anticoagulation is begun.

   All of the following are true EXCEPT

   a. Treatment should last for 3–6 months at a minimum
   b. The development of post-thrombotic syndrome may be minimized with the use of graduated compression stockings after anticoagulation is begun
   c. Placement of a permanent filter for the inferior vena cava will reduce the risk of complications in this patient
   d. Painful venous plethora of the leg should be treated as a vascular emergency
   e. Thrombosis of the left leg may be due to a congenital anomaly of the venous drainage of the limb.

   3. Answer c. Vena cava filters have very specific indications for patients with venous thrombosis, and should be removed as soon as the risk period has passed. Permanent implantation of filters is ineffective in reducing the long term VTE risk, and also may increase the risk for filter-relatedcomplications.

   All other statements are true: anticoagulation, though individualized for each patient, should continue a minimum of 3 months, and probably longer. Compression stockings may reduce the risk for painful edema of the limb after resolution of the DVT, while phlegmasia cerulea dolens is a vascular emergency, due to risk of venous gangrene. Lastly, the May-Thurner anomaly is a congenital compressive syndrome of the left-sided iliac vein, which increases the risk for spontaneous and recurrent venous thrombosis of this vessel.

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CHAPTER 14

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Diseases of the Aorta

CHAPTER OUTLINE

ABBREVIATIONS

AAA	Abdominal aortic aneurysm
ACC/AHA	American College of Cardiology/American Heart Association
ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AI	Aortic insufficiency
AS	Aortic stenosis
AV	Aortic valve
AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
BP	Blood pressure
bpm	Beats per minutes
CABG	Coronary artery bypass graft
cm	Centimeter
CT(A)	Computed tomogram (angiography)
CXR	Chest X-ray
dP/dt	Change in pressure over change in time, which is a measure of left ventricle ejection impulse, an index of shear stress on the aortic wall
DTAA	Descending thoracic aortic aneurysm
EVAR	Endovascular aortic aneurysm repair
GCA	Giant cell arteritis
HF	Heart failure
HR	Heart rate
IMA	Inferior mesenteric artery
IMH	Intramural hematoma of the aorta
IRAD	International Registry of Acute Aortic Dissection
LDL	Low density lipoprotein
LR	Likelihood ratio
M:F	Male to female ratio
mmHg	Millimeters of mercury
MMP	Matrix metalloproteinase
MR	Magnetic resonance

PAD	Peripheral artery disease
PAU	Penetrating atherosclerotic ulcer of the aorta
SBP	Systolic blood pressure
SD	Standard deviation
SMA	Superior mesenteric artery
STS	Society of Thoracic Surgeons
SVC	Superior vena cava
TAA	Thoracic aortic aneurysm
TAAA	Thoracoabdominal aortic aneurysm
TEE	Transesophageal echocardiography
TEVAR	Thoracic endovascular aortic repair
TGF	Transforming growth factor
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography
USPSTF	United States Preventive Services Task Force

AORTIC ANATOMY

- The largest artery in the body; muscular; retroperitoneal
- Histologically contains three layers:
  - Intima (endothelium supported by internal elastic lamina)
  - Media (smooth muscle cells and numerous elastic fibers that give the aorta remarkable tensile strength)
  - Adventitia (collagenous support matrix with external elastic lamina; site of entry of the vasa vasorum externae)
- The segments of the aorta are differentiated by their anatomic location, size, and branch vessels (Table 14-1). Dimensions in males are slightly larger than in females, and the aortic diameters generally increase with age.

TABLE 14-1

AORTA ANATOMY

AORTIC SEGMENTS	DIVISIONS	APPROXIMATE DIAMETERS	MAJOR BRANCH ARTERIES
Ascending			
	Root (sinuses of Valsalva)	≤4.0 cm	Right and left main coronary arteries
	Ascending aorta	≤3.5 cm	None
Arch		≤3.0 cm	Brachiocephalic (innominate), left subclavian, and left common carotid arteries
Descending		≤2.5 cm	Intercostal, spinal, bronchial arteries
Abdominal			
	Suprarenal	≤2.0 cm	Celiac axis, SMA, and renal arteries
	Infrarenal	≤2.0 cm	IMA, common iliac arteries

GENERAL HISTORY AND PHYSICAL EXAMINATION

- **Relevant history**:
  - Due to aorta: Look for chest, back, abdominal, flank pain or discomfort.
  - Due to complications of aortic disease:
    - Depends on the segment of the aorta affected and branch vessels and distal organ territories that are impacted.
    - Look for neurologic symptoms, syncope, heart failure, myocardial infarction, renal failure, thromboembolic disease, compression of adjacent structures such as nerves, esophagus or tracheobronchial tree.
- **Past medical history**: aortic disease, vascular disease, hypertension (HTN), thromboembolic events, trauma.
- **Family history**: aortic disease.
- **Physical examination**:
  - Check bilateral blood pressure (BP) and pulses (radial, carotid, femoral), pulsus paradoxus.
  - Look for evidence of aortic insufficiency (AI), tamponade, heart failure, neurologic deficits, and/or pulsatile abdominal mass.

IMAGING MODALITIES

Chest Radiography (CXR)

- CXR has overall limited sensitivity (~30–60%) for aortic diseases, and alone cannot be used to exclude acute or chronic aortopathy.
- Calcification or tortuosity of the ascending, arch, and descending thoracic aorta may be visualized, but this is a non-specific finding in the elderly.
- Opacification of the aorticopulmonary window, enlargement of the thoracic aorta, increased mediastinal width, displacement of trachea from midline, or obscured/irregular aortic margin may indicate thoracic aortic aneurysm, dissection, or rupture.
- Displaced intimal calcium and pleural effusion may indicate dissection.

Echocardiography and Ultrasonography

- Portable, avoids radiation and contrast media, and can be deployed intra-operatively.
- **Transthoracic Echocardiography (TTE)**
  - TTE cannot provide a comprehensive exam of the aorta, but certain regions can be visualized: aortic valve and root, ascending aorta, arch, descending, and abdominal aorta.
  - TTE is reasonable for assessing aortic valve disorders and monitoring aortic root and ascending aortic dilatation (e.g. especially in Marfan syndrome). It is not sensitive enough to rule out thoracic aortic dissection (sensitivity 70%).
- **Transesophageal Echocardiography (TEE)**
  - TEE can visualize the ascending aorta, transverse arch, and entire descending thoracic aorta. The distal ascending aorta and proximal aortic arch may be obscured by the trachea.

  - TEE, in contrast to other modalities, can provide functional information such as flow dynamics in true and false lumens, detection of AI, detection of cardiac tamponade, and assessment of left ventricular function.

- **Abdominal ultrasonography** is the technique of choice for screening for infrarenal abdominal aortic aneurysm (AAA), but is less accurate as applied to the suprarenal aorta or branch vessels.

Computed Tomography (CT)

- CT is a highly accurate, rapid, reproducible, and readily available technique for detecting and sizing aortic aneurysms and for the diagnostic evaluation of suspected aortic dissection.
- CT is also helpful at mapping branch vessels, and for detecting mimics of aortic disease (e.g. pericardial disease, gastrointestinal disease).

Magnetic Resonance (MR) Imaging

- MR is also a highly accurate technique for aortic imaging. However, the study time is lengthy and the patient is relatively inaccessible, making this modality unsuitable for acute or unstable patients.
- MR is most often performed with intravenous gadolinium as a contrast agent, but the "black-blood" technique with spin-echo sequences can provide satisfactory images without the need for gadolinium.

Aortography

- Catheter-based aortography is an invasive technique that can demonstrate the full extent of aneurysmal disease and dissection, map branch vessel involvement, and demonstrate the presence of AI.
- However, aortography is not readily available in most settings, requires an expert physician operator, and requires that potentially unstable patients undergo a prolonged procedure.

AORTIC ANEURYSMS

Definitions

- Aneurysm = dilatation of the aorta involving all three vessel wall layers.
- Pseudoaneurysm = contained leak of blood in communication with vessel.
- Fusiform = symmetric circumferential bulging of the aorta.
- Saccular = asymmetric localized bulging of the aortic wall.

Abdominal Aortic Aneurysms (AAA)

- **Epidemiology**:
  - Up to 3% prevalence >50 years, and 5% >65 years, with M:F ratio up to 10:1 [1].
  - Infrarenal AAA represents the most common location.
- **Etiology** [2]:
  - Chief pathophysiologic factors are atherosclerosis and smoking. Male gender, advanced age, dyslipidemia, and family history also contribute.
  - Inflammation, both primary or secondary to atherosclerosis, is increasingly recognized as a key factor that results in oxidative stress in the aortic media, deterioration of aortic tensile properties, and apoptosis of smooth muscle cells.

- There is an increased prevalence of AAA among first-degree relatives of affected individuals. Genetic basis is still unclear (may include structural proteins, proteases such as matrix metalloproteinases (MMP), or immunomodulatory genes).
- Bacteria and mycobacteria can generate infectious (also known as mycotic) aneurysms.

■ **History and Examination** [3, 4]

- Most AAA are asymptomatic, and diagnosed on physical examination or incidentally on imaging.
- Patients may have persistent pain in the lower abdomen or lower back, with a "gnawing" character.
- New or worsening pain may herald AAA expansion or rupture.
- Classic triad of AAA rupture = pain, hypotension, and pulsatile abdominal mass.
- Space-occupying effects of AAA include extremity ischemia, gastrointestinal or ureteral obstruction.
- Palpation of a pulsatile mass may help detect AAAs large enough to merit repair (sensitivity 68%, positive predictive value 43%), but alone is not sufficient to exclude AAA.
  - ■ Sensitivity correlates with AAA diameter (61% for 3.0–3.9 cm, 82% for > 5.0 cm), but sensitivity decreases with obesity.
  - ■ Palpation maneuvers for AAA are not believed to cause rupture.
- Auscultation of bruits does not help diagnose AAA.

■ **Screening and Diagnosis**

- Screening by exam and ultrasound is recommended by American College of Cardiology (ACC)/American Heart Association (AHA) (class I in 2006 guidelines) for males above age 60 who are siblings or offspring of parents with AAA.
- The United States Preventive Services Task Force (USPSTF) recommends abdominal ultrasonography screening for infrarenal AAA in all males age 65–74 who have ever smoked (ACC/AHA 2006 guidelines IIa recommendation)
- There are no recommendations for screening females or older males.

■ **Prognosis**:

- Risk of rupture varies with size. Annual risks are 0.3% for AAA diameter <4.0 cm, 1.5% for 4.0–4.9 cm, and 6.5% for 5.0–5.9 cm [5].
- Females with AAA have a greater risk of rupture than males, and experience rupture at smaller AAA diameters.
- Overall mortality from AAA rupture >50–80%.
- Mural thrombus within an AAA is associated with increased rates of growth and cardiovascular events.

■ **Medical Treatment**:

- Smoking cessation and lipid control (LDL goal <70 mg/dL) is essential.
  - ■ Studies of statins in AAA suggest possible reduction in AAA growth.
- Aspirin, reduction in BP, and reduction of dP/dt are reasonable.
- Beta-blockers carry a IIa recommendation for reducing the rate of AAA growth. For repair of atherosclerotic AAA, perioperative beta-blockade has a class I indication.
- Angiotensin converting enzyme inhibitors (ACEI) may, in addition to BP reduction, reduce rate of AAA rupture.
- Several studies have hinted a role for macrolide and tetracycline antibiotics based on a possible effect on Chlamydia (previously thought to be important in AAA pathogenesis), and for anti-inflammatory and anti-metalloproteinase properties. However, such therapies are not yet recommended for clinical use.

- **AAA Repair** [3]:
  - **Indications**: given high mortality from ruptured AAA, **prophylactic repair should be undertaken when infrarenal AAA is ≥5.5 cm. Infrarenal AAA of 4.0–5.4 cm should be re-imaged every 6–12 months.**
    - Size threshold may be smaller in females, in those with small body habitus, or those with family history of AAA or rupture.
    - Growth velocity >0.5 cm/year may be an indication for repair.
    - Symptoms always constitute an indication for repair.
    - Suprarenal AAA (or thoracoabdominal aneurysms, see below) may be repaired at sizes of 5.5–6.0 cm.
  - **Surgical repair of AAA**
    - Resection of aneurysm and replacement with a synthetic graft.
  - **Endovascular aortic aneurysm repair (EVAR)** [6–8]
    - Percutaneous fluoroscopically-guided deployment of an expanding endovascular stent inside the aneurysm and attached to the aorta at the proximal and distal aneurysm margins, thereby excluding the aneurysm from aortic blood flow.
    - Only about half of AAA patients have anatomy suitable for EVAR: anatomic considerations include aneurysm length, proximal and distal landing zones, tortuosity, aneurysm thrombus or calcium, iliac artery diameter.
    - EVAR reduces peri- and immediate post-procedure morbidity and mortality and post-operative hospitalization, but whether the long-term outcomes are improved or are as durable as open surgical repair remains under investigation. Randomized trials suggest no difference in long-term mortality (EVAR-1 and DREAM trials), although a single retrospective Medicare analysis from 2012 suggests higher all-cause mortality at 2.5 years from open repair vs. EVAR [9].
    - Endoleak: EVAR is associated with endoleak, or persistent blood flow into the aneurysm sac due to inability to completely exclude it from circulation.
    - Post-EVAR patients require imaging surveillance at 1, 6, and 12-months, in order to monitor for endoleaks, assess graft position, check aneurysm sac size, and gauge need for reintervention (class I).
    - Repair endoleaks that leak into aneurysm sac around an imperfect seal at proximal and/or distal anastomosis of stent graft OR structural defect, e.g. tear, stent fracture, etc.
    - EVAR patients have an approximately 10% higher reintervention rate at 6 years compared to open repair.
  - The 2011 ACC/AHA guidelines on peripheral artery disease (PAD) give a class I recommendation for "open or endovascular repair of infrarenal AAAs" in "good surgical candidates."
    - There is a class IIa recommendation for open AAA repair in good surgical candidates who could not comply with surveillance imaging post-EVAR.
  - Due to short-term advantages, EVAR has been considered for higher risk patients (e.g. older, high perioperative risks). However, the EVAR-2 trial studied patients deemed "physically ineligible" to undergo open repair and found no improvement in all-cause mortality versus medical therapy alone.
    - The 2011 ACC/AHA PAD guidelines give EVAR a class IIb recommendation in high risk surgical patients (uncertain benefit in this group).

Thoracic Aortic Aneurysm (TAA)

- **Epidemiology**:
  - TAA is believed to be about one-third as common as AAA. Because TAA is a clinically silent disease, the incidence is estimated from autopsy series at 3–4%.
  - TAA is most commonly seen > age 50; the age of onset is earlier than for AAA.
  - Male:Female ratio is ~2:1, as compared to AAA which has a much higher ratio.
- **Anatomic location:**
  - Ascending aorta: 60%
    - Root aneurysms are associated with Marfan syndrome
    - Ascending aortic aneurysms are associated with bicuspid aortic valve or sporadic aneurysms.
  - Arch: 10%
  - Descending thoracic aorta: 40%
  - Thoracoabdominal (see below): <10%
  - Multiple aneurysms: <10%
- **Etiology** [10–12]:
  - HTN and atherosclerosis are the primary risk factor for non-syndromic descending and thoracoabdominal aneurysms.
  - For root and ascending aneurysms, medial degeneration is the final common etiopathologic pathway.
    - Medial degeneration may be acquired (e.g. HTN) or congenital (e.g. Marfan syndrome).
    - Medial degeneration (previously called cystic medial necrosis), involves smooth muscle cell apoptosis, elastic fiber degeneration (particularly important in Marfan syndrome), and subintimal spaces infiltrated with mucoid proteoglycan.
    - MMP's are also implicated.
  - Bicuspid aortic valve (AV) is the most common cardiac congenital anomaly (~1–2% population prevalence; Male:Female 3:1), and is associated with TAA, dissection, and coarctation [13].
    - Bicuspid AV is associated with aortic medial degeneration.
  - Genetic TAA syndromes:
    - *Marfan syndrome:* Besides thoracic aortopathy, manifestations include valvular, skeletal, and ocular pathology. The etiology is an autosomal dominant defect in fibrillin-1, a structural glycoprotein in the extracellular matrix of the aorta media. Fibrillin-1 is also involved in downregulating the activity of TGFβ.
      - Aortic root dilatation is present in 80% of Marfan adults. Aneurysms may also appear in carotid/other cerebral arteries and the abdominal aorta.
    - *Loeys-Dietz syndrome:* Mutations in the TGFβ receptor cause a syndrome of arterial tortuosity with hypertelorism, bifid uvula, and cleft palate.
    - *Ehlers-Danlos syndrome, type IV*: This autosomal dominant defect in type III procollagen affects large and medium arteries, causing carotid and vertebral dissections. It also causes characteristic facial features and also marked weakness of skin, gastrointestinal, and uterine structures.
    - *Familial thoracic aortic aneurysm syndrome:* These are found in 20% of those with unexplained TAAs. There is no one genetic defect to screen for.

- Syphilis, once a common infectious cause of saccular TAA, is now a rarity.
- Autoimmune conditions may be associated with aortitis and secondary TAA (see below).

■ **History and Examination** [11, 12]

- TAAs are in general asymptomatic, but patients may have chronic back or chest pain, with the location of pain related to anatomic location of TAA. A pulsating sensation may be reported.
- The space-occupying TAA can cause symptoms depending on location and the structure affected (Table 14-2).
- Aortic root or ascending aortic aneurysms may present with AI or even HF.
- TAA may erode into the spine or esophagus (ask about hemoptysis).
- TAA may present with thromboembolic phenomena, e.g. to cerebral, spinal, visceral, or extremity arteries.
- Acute pain may herald dissection or impending rupture.
  - ■ Location of pain has some correlation with anatomy: anterior pain with ascending TAAs, neck pain with arch aneurysms, interscapular pain with DTAA.

■ **Screening and Diagnosis**:

- Most TAA are recognized incidentally on CXR, CT, or TTE.
- TTE is recommended as the first test for assessment of the ascending aorta in known or suspected connective tissue disorders, or genetic conditions that predispose to TAA (2011 ACC/AHA Appropriate Use Criteria for Echocardiography) [14].
- There are no consensus guidelines on population screening for TAA.
- For first-degree relatives of patients with TAA, screening with echocardiography or CT is recommended.
- In patients with bicuspid AV, ACC/AHA 2006 valve guidelines give a class I recommendation for an initial TTE for assessment of aortic root and ascending aortic dimensions [15].
  - ■ If the TTE is insufficient to document morphology and dimensions, or ascending aortic dilatation is present, then CT or MR is reasonable.
  - ■ Bicuspid AV patients with root or ascending aorta >4.0 cm should have yearly imaging (though the size cutoff can be reduced for smaller stature patients).

■ **Prognosis** [10–12]:

- Growth velocity of TAA is variable but approximated at 0.5–5 mm/year; growth rates are higher for larger aneurysms and descending TAA.
- Annual risks of dissection or rupture vary with TAA size, from <2% for diameter <5.0 cm, 3% for 5.0–5.9 cm, and 6.9% for >6.0 cm.
  - ■ Patients with underlying connective tissue disease such as Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes experience rupture at smaller sizes.
- TAA rupture causes ~75% mortality at 24 h.

TABLE 14-2

SPACE-OCCUPYING SYMPTOMS OF TAA

AFFECTED STRUCTURE	RESULTANT SYMPTOMS
Coronary arteries	Chest pain
Trachea, bronchioles	Dyspnea, stridor, wheeze, cough
Esophagus	Dysphagia
Superior vena cava (SVC)	SVC syndrome
Recurrent laryngeal nerve	Hoarseness (Ortner's syndrome)
Spinal cord compression	Horner's syndrome, paraplegia

- **Surveillance imaging**
  - Once thoracic aortic pathology is detected, a full imaging evaluation of the thoracic aorta should be performed to document extent of disease and baseline aortic diameters.
  - ACC/AHA guidelines recommend annual imaging for following most aneurysms.
    - It is also reasonable to obtain the first follow-up imaging exam at 6 months after diagnosis to exclude rapid growth (as may be seen in aortitis).
    - Once a TAA growth trajectory is stable, ACC/AHA guidelines consider imaging every 2–3 years for smaller TAA in older patients.
  - Re-imaging should be considered for a change in clinical status or physical exam.
- **Medical management** [12]
  - The primary goals are to reduce dP/dt and BP in order to reduce aortic wall tension and reduce the risk of aortic dissection or rupture
  - Goal heart rate <60 beats per minute (bpm) and systolic BP <110–120 mmHg.
  - Trial data is limited [25, 26]:
    - Beta-blockers have been the mainstay of medical treatment for TAA. While beta-blockers have been demonstrated to reduce the rate of aneurysm growth in Marfan patients with large aneurysms, their efficacy in aneurysms of other etiologies has not been proven.
    - Losartan, an angiotensin receptor blocker, is also a TGFβ antagonist, and has been proven to dramatically reduce the rate of aneurysm growth in a mouse model of Marfan syndrome. Angiotensin receptor blockers have previously been shown to slow aneurysm growth in a small non-randomized study of children with Marfan syndrome. However, a recent randomized trial of losartan versus atenolol in children and young adults with Marfan's syndrome found no significant difference between rates of aortic root dilatation between the two treatment groups.
  - Burst precautions:
    - Patients should avoid activity or exertion that can acutely raise aortic wall stress.
    - Guidelines suggest avoiding heavy lifting or straining, i.e., isometric activities that would require the Valsalva maneuver.
- **TAA Repair** [11, 12]
  - **Indications**: Suggested criteria for elective TAA repair based on ACC/AHA guidelines include the following diameter thresholds:
    - **Repair of ascending TAA at a diameter of ≥5.5 cm, but at a lower diameter of ≥5.0 cm for those with Marfan syndrome or a familial thoracic aortic aneurysm syndrome, and at a diameter of ≥4.4 cm for Loeys-Dietz syndrome.**
      - For those with Marfan syndrome and bicuspid AV who have either a small or large body habitus, surgery is recommended when the ratio of the maximal root or ascending aortic cross-sectional area (in square centimeters) to patient height (in meters) is >10.
      - The 2016 revised ACC AHA guidelines raised the threshold for TAA repair back to **≥5.5 cm** for asymptomatic patients with bicuspid AV. Repair is still indicated at **≥5 cm** for bicuspid AV patients with additional risk factors (family history of dissection or rapid growth rate) for patients at low surgical risk [16].
    - Arch diameter ≥5.5 cm.
    - Descending TAA diameter ≥5.5–6.0 cm.
    - Rapid growth rate of a TAA >0.5 cm/year.

- In patients undergoing cardiothoracic surgery for another indication (e.g., coronary artery bypass graft (CABG), AV repair), an aortic root or ascending aortic diameter **≥4.5 cm** may be repaired.
- TAA symptoms are an indication for repair.

– **Open surgical approach**

- Ascending and arch TAA require median sternotomy, while descending TAA and thoracoabdominal aortic aneurysms (TAAA) are approached via left thoracotomy.
  - Surgical repair of descending TAA and TAAA are associated with significant morbidity, including risk of spinal cord ischemia and paraplegia. Various neuroprotective strategies help reduce spinal cord ischemia.
- Repair of arch aneurysms is usually performed with insertion of prefabricated branched graft and supported by antegrade cerebral perfusion.
- Root aneurysms used to require sacrificing the aortic valve and insertion of a valved-conduit (composite aortic graft or Bentall procedure). Now the aortic valve can usually be preserved and resuspended within the prosthetic graft (valve-sparing root repair or David procedure).
- In recent decades, overall surgical mortality has declined from 10–20% to approximately 5%.

– **Thoracic endovascular aortic repair (TEVAR)**

- For descending TAA, TEVAR is an alternative to open repair when anatomy is conducive.
- Akin to EVAR for AAA, TEVAR provides an upfront reduction in morbidity and mortality, but long-term mortality benefits are not proven.
- Although there are no randomized trials of TEVAR versus open repair, large registry and metaanalysis data (a mix of aneurysms and dissections) have been favorable. TEVAR is therefore now recommended for descending TAA ≥5.5 cm; the Society of Thoracic Surgeons (STS) recommends TEVAR as class IIa if there are comorbidities, and class IIb if no comorbidities.
- TEVAR also results in endoleak (12–18% incidence), and surveillance is therefore indicated at 1, 3, 6, and 12-months post-procedure.

Prevalence of Concurrent Aneurysms [17]

The presence of an aortic aneurysm is associated with increased prevalence of aneurysm at another location.

- About 1/4 of TAA patients have an AAA.
- Similarly, about 1/4 of AAA patients will have a TAA.
- Consider pan-aortic imaging initially in any patient with either AAA or TAA.
- Popliteal and iliac artery aneurysms are common in AAA/TAA patients.

Thoracoabdominal Aortic Aneurysms (TAAA)

TAAA involve the descending thoracic aorta and extend to the abdominal aorta.

- TAAA and its repair are classified by Crawford types.
  - Types I and II each involve the majority of descending thoracic aorta from the left subclavian artery, with Type I involving the proximal portion of the abdominal aorta and type II extending to the infrarenal abdominal aorta.

- Type III involves the distal descending thoracic aorta and below the diaphragm a large part of the abdominal aorta.
- Type IV involves the diaphragmatic aorta and most of the abdominal aorta.

■ TAAA repair is indicated at a diameter ≥5.5–6.0 cm.

ACUTE AORTIC SYNDROMES: AORTIC DISSECTION, INTRAMURAL HEMATOMA (IMH), PENETRATING ATHEROSCLEROTIC ULCER (PAU)

Patients with these syndromes present similarly regardless of mechanism.

Aortic Dissection

■ **Definition**: Penetration of blood from the aortic lumen into the medial layer of the aortic wall, due to a tear in the intimal layer, resulting in splitting the media into layers and creating a second channel for blood flow called the false lumen.

■ **Classification**: Because morbidity, mortality, and management are dictated by whether or not the dissection involves the ascending thoracic aorta, classification schemes have been designed to distinguish those that involve the ascending aorta from those that do not (see Fig. 14-1).

- *DeBakey Classification*: type I originates in ascending aorta and progresses to arch ± descending aorta; type II is confined to ascending aorta; type III originates in and is generally localized to the descending aorta.
- *Stanford*: type A involves ascending aorta regardless of origin; type B is distal to the ascending thoracic aorta.

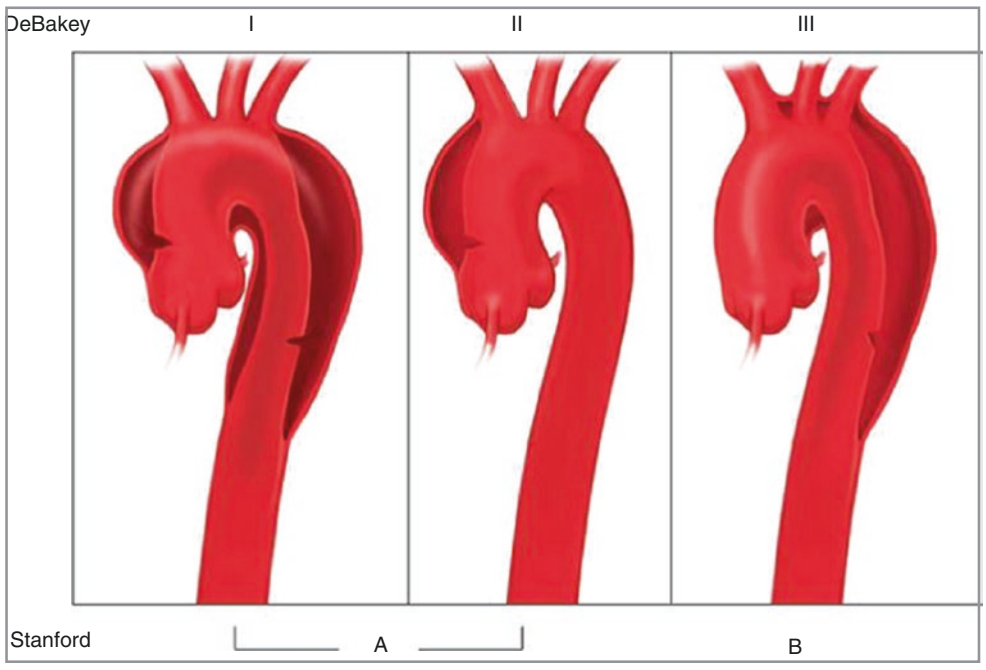

FIGURE 14-1

Classification systems for aortic dissection. © Massachusetts General Hospital Thoracic Aortic Center, used with permission

- **Epidemiology**: Estimated incidence of 2–16 cases per 100,000 person-years, but incidence likely underestimated due to early rapid mortality (out-of-hospital deaths attributed to other causes; misdiagnosis of aortic dissection).
  - Type A dissection is twice as common as type B.
  - Marfan syndrome accounts for approximately 5% of dissections, and up to 50% of patients under age 40.
  - Bicuspid AV accounts for more cases of dissection than Marfan syndrome; even though the risk of dissection per patient is less than in Marfan syndrome, the fact bicuspid AV has a prevalence of 1–2% makes it quantitatively an important cause of aortic dissection.
  - When aortic dissection occurs in women less than 40 years of age, 12% occur in the peripartum period of pregnancy.
- **Etiology**
  - Dissection is common at sites of aneurysm, and thus risk factors for aneurysm and dissection are similar, e.g. HTN, BAV, Marfan syndrome, family history of TAA or dissection.
    - However, dissection may occur in non-aneurysmal aortic segment.
    - Procedures that involve manipulation of the aorta (e.g., catheterization, intra-aortic balloon pumps, and cardiac surgery) may cause iatrogenic dissection.
    - Cocaine may trigger dissection.
    - Traumatic aortic injury typically causes aortic transsection but can cause dissection.
- **History and Examination** [11, 18, 19] (see Table 14-3)
  - Pain is the most common symptom of dissection (~90%). Evaluating characteristics of the pain by questions about onset, intensity, quality, and radiation can be very helpful, as physicians that asked these questions correctly identified dissection in ~90% of cases versus ~50% when a question was skipped.
    - Abrupt onset is reported in 84% of cases. It is typically maximal at onset, which is not typical in acute coronary syndromes.
    - Pain is characterized as severe in 90% of cases.

TABLE 14-3

SIGNS AND SYMPTOMS OF AORTIC DISSECTION

SIGNS AND SYMPTOMS	POSITIVE LR	SENSITIVITY (%)
Severe pain		90
Enlarged aorta or wide mediastinum on CXR	2.0–3.4	90
Sudden onset	1.6–2.6	84
AI murmur		45
Ripping or tearing	1.2–10.8	39
Radiating or migrating	1.1–7.6	31
Pulse or BP differential	5.7	26–31
Diastolic murmur	1.4	28
Neurological deficit	6.6–33.0	17
Syncope		13
Shock		13
Lower extremity ischemia		10
Stroke		6–8
Tamponade		5
Spinal cord ischemia		2

- The quality is classically thought to be "ripping" or "tearing" but "sharp" (51%) or "stabbing" (64%) pain is more often reported.
- Location of pain may correlate with that of the dissection, and migrates as the dissection propagates.
  - Type A dissections are twice as likely to have anterior versus posterior chest or back pain.
  - Type B dissections have back pain in 2/3 of cases, but chest pain may also occur.
  - Abdominal pain may be the sole manifestation of dissection, and pain may also be localized in neck, lower back, or extremities.
- The pain is often persistent, but it can abate.
- When pain is absent, patients usually present with syncope, stroke, or heart failure.

– Blood pressure

- At presentation, approximately one third of patients are hypertensive, while one seventh are hypotensive and one seventh are in shock.
- HTN is a more common presentation for Type B dissections.
- Hypotension in a type A dissection suggests severe AI, tamponade, or coronary ischemia.
- BP must be measured in both arms, and frequently needs to measured in both arms and both legs, in order to recognize pseudohypotension, or a spuriously low BP measurement due to dissection affecting the a branch artery.
- A BP differential of > 20 mmHg is considered significant.

– Syncope is seen commonly in type A dissection (19%) and uncommonly in type B (3%).
– Focal neurologic deficit is present in ~1/6 cases of thoracic aortic dissection.
– Whenever a constellation of cardiovascular, neurologic, and abdominal symptoms is otherwise unexplained, an acute aortic syndrome must be considered as a potential unifying diagnosis.

■ **Sequelae of Aortic Dissection**

– Hemopericardium resulting in pericardial effusion and potentially cardiac tamponade and shock.
– Acute AI, potentially causing heart failure or shock.
– Acute myocardial infarction (inferior more common than anterior, due to predilection of dissection to extend into right coronary artery)
– Dissection involving other branch arteries: Carotid (stroke or transient ischemic attack), spinal (paraplegia), renal (acute renal insufficiency), mesenteric (abdominal pain, mesenteric ischemia), or iliac arteries (lower extremity pain, ischemia).

■ **Diagnosis** [11, 18, 20]

– ECG and CXR are quick tests (especially for patients at low and intermediate risk of dissection) that may reveal an alternate explanation for the presenting symptoms. However, they cannot be used to rule in or out aortic dissection.
– To definitively diagnose or exclude aortic dissection, one should obtain a CT angiogram, a TEE, or an MR angiogram. In most settings CT is preferred. The ultimate choice of diagnostic tests depends on which modalities are readily available at a given institution and the expertise with which a test can be performed and interpreted.
– When clinical suspicion for dissection is quite high, one negative imaging modality (CT, TEE, or MR) may not be sufficient to fully exclude the diagnosis, and the evaluation should include a second confirmatory test (ACC/AHA guideline, class I).
– Biomarkers: D-dimer alone cannot be used to exclude aortic dissection as the negative predictive value is only ~97% however it can be helpful in cases where the probability of dissection is already low. The D-dimer can be normal in causes of intramural hematoma.

- **Prognosis**
  - Type A
    - Immediate death rate may be as high as 40%.
    - Mortality is estimated at 1–2% per hour after dissection.
    - Death is commonly related to hemopericardium and tamponade, rupture, or propagation of dissection. Survival can be improved with early recognition and treatment.
  - Type B
    - Overall 30-day mortality is 10% for uncomplicated patients managed medically but rises to 30% among patients with complications who require surgical treatment.
- **Treatment of type A dissection** [11, 21]
  - Urgent surgical repair is indicated for acute type A dissections.
  - The goal of surgery is to replace the dissected ascending aorta, in order to prevent death from aortic rupture.
  - The aortic arch is typically not repaired in the acute setting, unless the arch is significantly dilated or the intimal tear is located within the arch.
  - Preoperative coronary angiography is typically not indicated as it causes an unnecessary delay in aortic repair.
  - Medical therapy should be instituted while awaiting operative repair.
  - dP/dt reduction and HR goal <60 represent primary goals, with secondary goal SBP <100–120 mmHg (or to the minimum level that preserves perfusion).
  - IV beta-blockade should be started first, so as to avoid reflex tachycardia (and thus increased dP/dt) from vasodilator therapy. Propranolol, metoprolol, esmolol, or labetalol are all reasonable; when beta-blockers are contraindicated, IV diltiazem or verapamil should be considered.
  - Sodium nitroprusside can also be used for rapid reduction and careful titration of BP.
  - Analgesia is necessary to blunt pain-related increases in HR and BP.
  - Hypotension: If due to tamponade, the treatment is volume resuscitation and emergent surgery; pericardiocentesis is not helpful and in fact associated with increased mortality (and should only be considered en route to the operating room or after cardiopulmonary bypass is established, unless the patient is in arrest).
- **Treatment of type B dissection**
  - Uncomplicated type B dissection is managed medically with reduction of dP/dt and BP, as detailed above.
  - Intervention is indicated for complications, including malperfusion syndromes, refractory pain, refractory HTN, enlarging aneurysms, or rupture.
  - Endovascular intervention is now generally preferred over open surgical repair to treat complicated type B dissections because they are associated with a significant lower 30-day mortality.
    - However, the long term impact of stent-grafting an acutely dissected descending aorta remains unknown.
    - In has been theorized that early stent-grafting of uncomplicated type B dissections might serve to prevent potential late complications or aneurysm expansion, and a randomized trial is underway, but at present there are no data to support such a strategy.
- **Late complications**: Patients are at risk and must be followed for aneurysm formation, recurrent dissection, rupture, AI (for those involving the root or ascending aorta), and endoleak (following TEVAR procedures).

- The highest risk is in the first 1–2 years.
- Medications to reduce dP/dt and control HTN can reduce the rate of complications. The goal is a HR of <60 and a SBP of <120.
  - Beta-blockers have been shown to improve late outcomes and therefore represent the mainstay of chronic therapy.
  - Calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers may also be of benefit but the data are unclear.
- Because of the risk of progressive aortic growth following acute aortic dissection, patients should undergo serial surveillance imaging at intervals of 1, 3, 6, and 12-months and then annually thereafter, if stable.

Intramural Hematoma (IMH) [22]

- **Definition**: Bleeding contained within the media of the aortic wall but without communication with the aortic lumen.
- **Etiology**: Some may be due to rupture of the vasa vasorum within the aortic wall, whereas others appear secondary to microscopic intimal tears.
- **Epidemiology**: The risk factors are similar to those of aortic dissection, although it is less commonly seen among those with Marfan syndrome.
  - IMH accounts for 6–10% of acute aortic syndromes.
  - The descending aorta is affected in 60% of cases.
- **History and Examination:** clinical presentation is similar to classic aortic dissection.
- **Diagnosis**: IMH is diagnosed using CT, MR, or TEE.
  - Unlike classic aortic dissection, there is no intimal flap or blood flow within the aortic wall. Instead, IMH appears as a crescentic or circumferential thickening of the aortic wall. The presence of thrombus in the aortic wall has higher intensity on CT scanning, and does not enhance with contrast. Aortography can easily miss IMH.
- **Treatment and prognosis** and similar to classic aortic dissection.
  - IMH may convert to classic dissection in ~10% of cases.
  - Surveillance imaging after an acute IMH is similar to classic dissection.

Penetrating Atherosclerotic Ulcer for the Aorta (PAU)

- **Definition**: An atherosclerotic plaque breaches the internal elastic lamina, allowing blood to penetrate the wall to a varying degree.
- **Epidemiology**: PAUs are most prevalent in older patients with a history of atherosclerosis, HTN, and smoking.
- PAUs appear most often in the mid-to-distal descending thoracic aorta (90%) due to the prevalence of atherosclerosis in this segment.
- PAU may convert to typical dissection, IMH, a saccular aneurysm, or pseudoaneurysm, which in turn may lead to rupture.
- **Treatment**: Small PAUs are managed medically with antihypertensives and surveillance imaging. Large or expanding PAUs, or ulcers that have caused pseudoaneurysms, may require intervention, and TEVAR is generally preferred given that this population tends to be older and at high risk from open repair.

Aortic Transsection

- **Definition**: Through-and-through tear involving all three layers of the aortic wall. It may be partial or complete, in which case the aorta is completely severed. Such injuries may lead to fatal exsanguination, but in some cases the patient survives because the bleeding is contained by a pseudoaneurysm.
- Traumatic aortic tears result from deceleration injuries, and therefore typically occur near anatomic sites at which the aorta is anchored in the chest, i.e., the ligamentum arteriosum and aortic root.
- **Diagnosis** is most readily and accurately made by CT angiography.
- **Treatment**: intervention is required: For tears near the ligamentum, TEVAR is the treatment of choice; for tears in the aortic root open cardiac, surgery is required.

VASCULITIDES INVOLVING THE AORTA [23]

Giant Cell Arteritis (GCA)

GCA, also known as temporal arteritis, occurs most often in those older than age 50 (especially among those >75 years old). Women outnumber men 2:1, and it is more common among those with northern European ethnicity.

- It affects elastic arteries, including the aorta and extracranial (but not intracranial) arteries.
- Polymyalgia rheumatica, an inflammatory condition characterized by constitutional symptoms and shoulder and hip pain and stiffness, is found in about half of patients with GCA.
  - Approximately 15% of patients with polymyalgia rheumatica have GCA.
- Constitutional symptoms including malaise, anorexia, weight loss, and fevers are common.
- Aortic aneurysms: More than 10% can develop thoracic aneurysm as a late manifestation.
- Therefore surveillance imaging is recommended for up to 10 years after onset.
- **History and Examination**: mainly due to arterial occlusion:
  - Temporal artery: Ocular symptoms (double or blurry vision may precede permanent blindness), temporal headache, jaw claudication, scalp tenderness.
  - Vertebral artery: Symptoms of vertigo, dizziness, cerebellar signs, stroke.
  - Axillosubclavian arteries: Symptoms of arm claudication, absent pulse.
- American College of Rheumatology diagnostic criteria include: age >50, new headache, temporal artery tenderness or diminished pulse, erythrocyte sedimentation rate >50 mm/h, necrotizing vasculitis on biopsy.
- **Treatment**:
  - Corticosteroids are the principal treatment of GCA; therapy over 1-2 years is used to prevent recurrence.
  - Biopsy should not delay initiation of steroids when GCA is suspected; the biopsy will have reasonable yield even within a few days of starting steroids.
  - Other immunomodulators are as efficacious as corticosteroids.

Takayasu Arteritis

- Takayasu arteritis, sometimes referred to as "pulseless disease," is an idiopathic granulomatous vasculitis affecting large and medium sized muscular arteries (aorta, brachiocephalic arteries, pulmonary artery).
- Takayasu arteritis is most common in women (Male:Female ~1:10) in the second to third decades. Takayasu arteritis is more common in East Asia and Africa than in Europe or North America.
- Takayasu arteritis follows an early inflammatory stage (marked by a non-specific systemic inflammatory state with fever, sweats, and weight loss) followed by a later sclerosing phase.
  - The non-specific initial stage results in delayed diagnosis so that 90% of patients present in the sclerotic phase at diagnosis.
  - Arteritis can manifest as stenosis or aneurysm, and aortic involvement may be patchy.
- **History and Examination**: vary by affected artery
  - Aorta: AI, myocardial ischemia or infarction due to stenoses of the coronary artery ostia.
  - Subclavian: Decreased upper extremity BP (or a BP differential), pain in upper extremities, bruits.
  - Carotid: Amaurosis fugax, stroke.
  - Renal: Marked HTN.
- **Diagnosis**:
  - Diagnostic criteria from the American College of Rheumatology include intermittent claudication, diminished pulses, subclavian bruits, BP differential, and angiographic evidence of aortic or branch vessel stenoses.
  - Angiography can reveal both stenoses and aneurysms.
- **Treatment**:
  - High dose corticosteroids are the mainstay of treatment and the treatment course may need to extend 1–2 years. ACC/AHA recommends periodic monitoring of disease activity by exam and/or inflammatory markers.
  - Cyclophosphamide, azathioprine, methotrexate, or tumor necrosis factor inhibitors may be used in cases where either systemic inflammatory symptoms recur, vascular disease continues to progress, or inflammatory markers rise.
  - Surgical bypass (or reconstruction) and balloon angioplasty are options to treat severe arterial stenoses.

IgG4-Related Disease [24]

- IgG4-related disease is an autoimmune condition characterized by overproduction of IgG4 with lymphoplasmacytic and eosinophil tissue infiltrate, obliterative phlebitis, and fibrosis.
- IgG4-related disease affects a number of glandular tissues but a lymphoplasmacytic aortitis has been described that may generate aneurysm and dissection.
- In a single center experience, IgG4-related disease caused approximately 9% of non-infectious thoracic aortitis.

TABLE 14-4

QUICK REVIEW

FINDINGS	IMPLICATION
Elderly male, abdominal pain, pulsatile mass	AAA rupture
Ehlers-Danlos syndrome type IV	Risk of ascending aortic aneurysms
Loeys-Dietz syndrome	Mutations in the TGFβ receptor; treat with losartan
dP/dt	Principle to reduce wall stress by reducing HR and BP
Marfan syndrome	High risk for aortic root aneurysms and dissection
DeBakey classification system	Types I and II involve the ascending aorta
Stanford classification system	Type A involves the ascending aorta
Histologic pattern in aneurysm wall	Medial degeneration
Laplace's Law	Wall tension proportional to product of pressure and radius
Type A aortic dissection	High risk of rupture, tamponade, and death
Genetic defect in Marfan syndrome	Mutation in *FBN-1*, the gene for fibrillin-1
Prevalence of BAV	1–2% of the general population
Pseudohypotension	Falsely low BP in due to compromise of branch artery in aortic dissection
Intramural hematoma	Blood in aortic media that does not communicate with aortic lumen
Syndrome associated with giant cell arteritis	Polymyalgia rheumatica
Hoarseness	Recurrent laryngeal nerve compression (Ortner's syndrome) by a large TAA
Myocardial infarction in aortic dissection	Type A dissection with compromise of the right coronary artery ostium
Paraplegia after descending thoracic aortic aneurysm repair	Major risk associated with surgery on the descending or thoracoabdominal aorta
Bicuspid valve repair indicated at ≥5.5 cm if asymptomatic	Repair safe to be delayed for asymptomatic patients
Aortic injury following a motor vehicle accident	Deceleration injury causing aortic transsection; most often occurs at ligamentum arteriosum
Circle of Willis aneurysm in aortic dissection patient	Coarctation of the aorta is the likely underlying lesion

QUICK REVIEW (TABLE 14-4)

Questions and Answers

1. A 41 year old female acquaintance was evaluated for a heart murmur. On exam she had a systolic ejection click and faint systolic ejection murmur. An echocardiogram reported a bicuspid aortic valve with a horizontal commissure and, but the valve functioned well and there was no stenosis and trace aortic insufficiency. Her aortic root diameter was 3.6 cm. Her cardiologist reassured her that there is nothing further to do and she should simply follow-up with her internist annually. She is anxious and has therefore called you for advice. What is the most prudent suggestion to offer?

A. The cardiologist's plan is sound, so she should follow up with her internist.
B. She should undergo genetic testing for a mutation in the gene for fibrillin-1.
C. Her first degree relative should be screened for thoracic aortic aneurysms.
D. She should undergo a CT or MR to determine if her ascending thoracic aorta is dilated.
E. She should undergo annual surveillance echocardiograms to monitor her bicuspid aortic valve function.

1. Answer D. The echocardiogram documented a normal aortic root diameter, but no mention was made of the size of the ascending thoracic aorta. The aortic root and ascending thoracic aorta are distinct anatomically, and one aortic segment may be enlarged while the other is normal in size. Therefore unless both diameters are documented in the report as normal, a dilated aorta cannot be excluded. Half of those with bicuspid aortic valve have a dilated proximal aorta, and the majority of such aneurysms involve the ascending aorta rather than the root, so in any patient diagnosed with a bicuspid aortic valve the ascending thoracic aortic diameter must be evaluated. Since this echocardiogram apparently did not exclude a dilated ascending aorta another imaging study, either a CT or MR, should be obtained. There is no indication to test for the fibrillin-1 mutation in the setting of bicuspid aortic valve, as this is an abnormality associated with Marfan syndrome. The patient has a bicuspid aortic valve but has not yet been found to have a TAA, so there is yet no indication to screen her first-degree relatives for aneurysms. Her bicuspid aortic valve functions well, so there is no indication for annual surveillance echocardiograms to monitor the valve.

2. A 66 year old male new to your practice has a past history of uncontrolled HTN and a descending thoracic aortic aneurysm, and four months ago suffered a type B aortic dissection that was managed with TEVAR. Which of the following is not endorsed in ACC/AHA guidelines for this patient?
   A. Chronic beta-blocker therapy
   B. Surveillance imaging of the thoracic aorta at 1, 3, 6 and 12 months following the aortic dissection.
   C. D-dimer to assess for degree of thrombosis of false lumen.
   D. Pan-aortic imaging to exclude e.g. a concurrent AAA.
   E. Burst precautions.
   F. All of the above are indicated or recommended.

2. Answer C. The 2010 ACC/AHA guidelines on thoracic aortic disease highlight beta-blockade as an integral therapy for patients following aortic dissection. Serial imaging is recommended at regular intervals following an acute dissection given the risk of rapid early growth of dissected segments of the aorta. Burst precautions, or avoiding heavy lifting, straining, or pushing that would raise aortic pressure, is prudent. Because of the prevalence of concurrent aneurysms, patients with either TAA or AAA should have the entire aorta imaged on at least one occasion. While degree of thrombosis of a false lumen of a type B dissection correlates with mortality, D-dimer testing is neither helpful nor indicated in this context.

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CHAPTER 15

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Supraventricular Arrhythmias

CHAPTER OUTLINE

BASICS

- Supraventricular arrhythmias are abnormal heart rhythms that originate in the atria or in the conduction system proximal to or within the Bundle of His
  - Atrial arrhythmias
  - Junctional arrhythmias
- May be broadly divided into
  - Bradyarrhythmias (rate <60 [or 50] beats per min (bpm))
  - Tachyarrhythmias (rate >100 bpm)
  - Ectopic rhythms at physiologic heart rates—originating at a non-sinus site of impulse formation
- Many, but not all supraventricular arrhythmias can be diagnosed on the 12-lead surface electrocardiogram (ECG)

Sick Sinus Syndrome (SSS; Tachy-Brady Syndrome)

- Due to SA nodal and atrial electrical dysfunction
- In the brady-tachy variant of SSS, atrial bradyarrhythmias may alternate with tachyarrhythmias including
  - Atrial fibrillation (AF)
  - Atrial flutter (AFL)
  - Other supraventricular/atrial tachycardias (SVT)
- Although coronary heart disease (CHD) is commonly present in patients with SSS, the SA nodal artery may be normal in coronary arteriograms
- AV nodal disease and increased risk for thromboembolism may be present
- Over time (years), the patient may develop paroxysmal, then persistent AF
- Long pauses may be observed after conversion of tachyarrhythmias (post-conversion pause)
  - Such pauses may be accompanied by syncope (Stokes-Adams attacks, as well as pause-potentiated lengthening of the QT interval, with attendant risk for ventricular arrhythmia)
- Bradyarrhythmias may facilitate the occurrence of reentrant tachycardias by magnifying discrepancies in the duration of refractoriness as occurs with longer cycle lengths

TACHYARRHYTHMIAS

- Supraventricular tachyarrhythmias (SVT) may be due to reentry, enhanced automaticity or triggered activity
- Demonstrate a narrow (<120 ms) QRS unless there is aberrant intraventricular conduction, preexisting BBB, or accessory pathway
- Narrow QRS tachyarrhythmias:
  - Sinus tachycardia (ST)
  - Inappropriate sinus tachycardia (IST)
  - Sinoatrial nodal reentrant tachycardia (SNRT)
  - Atrial tachycardia (AT)
  - Atrioventricular nodal reentrant tachycardia (AVNRT)
  - Atrioventricular reentrant tachycardia (AVRT)
  - Non-paroxysmal junctional tachycardia (NPJT)
  - Atrial fibrillation (AF)
  - Atrial flutter (AFL)
  - Multifocal atrial tachycardia (MAT)
- Narrow QRS tachyarrhythmias may be divided into three categories depending on the structures needed for their maintenance (and initiation):
  - ST, IST, and SNRT require the SA node
  - AVNRT and AVRT require the AV node
  - AT, AF, AFL, and MAT require only atrial tissue

Sinus Tachycardia (ST)

- Sinus rhythm with a heart rate >100 bpm at rest is usually due to normal sympathetic activation such as in exercise, anxiety, fever, etc.
- ST may also be due to hyperthyroidism, chronic pulmonary disease, pulmonary embolism, severe anemia, hypovolemia and many other causes (sepsis, pheochromocytoma, stimulant drugs)

- Elimination or amelioration of the underlying cause is only treatment needed in the great majority of cases
- BB are indicated in rare instances (e.g. in angina, acute myocardial infarction)

Inappropriate Sinus Tachycardia (IST)

- IST is ST occurring in persons with structurally normal hearts in the absence of a physiologic or pharmacologic stimulus for tachycardia such as hyperthyroidism, severe anemia, or other causes of ST mentioned above
- Autonomic imbalance, increased beta-adrenergic sensitivity, abnormal sinus node automaticity are present in these patients
  - Most patients have both high resting heat rates and marked increase in rate with mild exercise
- Slow exercise conditioning, BB, ivabradine, and sinus node modification (catheter ablation) have been used for therapy, although catheter ablation is rarely recommended
- Postural Orthostatic Tachycardia Syndrome (POTS) is a related condition characterized by marked increase (>30 bpm or to 120 bpm) of the sinus rate with or without orthostatic hypotension upon assuming the standing position
  - Can be observed with dehydration, hypovolemia after prolonged bed rest
  - In idiopathic forms, distal (lower extremity) denervation, increased sympathetic activity, hypovolemia, and abnormal baroreflex function may be present
  - Treatment includes increased salt and water intake, mineralocorticoids (e.g. fludrocortisone), or adrenoreceptor agonists (e.g. midodrine)

SA Nodal Reentrant Tachycardia (SNRT)

- An uncommon supraventricular tachyarrhythmia with abrupt onset and offset where reentry occurs within the SAN or between the SAN and the surrounding perinodal tissue
- The configuration of the P waves is normal
- Heart rates between 100 and 150 bpm are typical
- Therapy is usually not necessary
  - In severe cases, vagal maneuvers, adenosine, BB, or CCB can terminate the arrhythmia
  - BB and CCB may used for prevention
  - When both the arrhythmia and the medications are not tolerated, SAN ablation or modification may be used, although this is rarely recommended

Atrial Tachycardia (AT)

- Focal AT are usually paroxysmal, though incessant forms exist
- May be due to reentry, abnormal automaticity or triggered activity [1]
- Commonly originate in the RA (frequently from the crista terminalis) or in the pulmonary veins or other areas within the LA
- Rates vary between 130 and 250 bpm and the P wave configuration depends on the site of origin of the arrhythmia
- Treatment includes correction of precipitating abnormalities (hypokalemia, digoxin), vagal maneuvers, and adenosine (usually not effective), BB, non-dihydropyridine CCB in stable patients, and class I and III membrane-active antiarrhythmic drugs
- Example: Chapter 33, ECG #35

Multifocal Atrial Tachycardia (MAT)

- Typically occurs in older patients with pulmonary disease [2]
- There must be distinct P waves of at least three configurations (may include the sinus configuration) associated with varying (at least three) PP intervals, PR intervals, and RR intervals
- Treatment includes correction of electrolyte abnormalities, therapy for the underlying precipitating disease
- BB and CCB and antiarrhythmic drugs may be helpful in some cases
- Multifocal atrial rhythm (60–100 bpm) and multifocal atrial bradycardia (<60 bpm) may also occur
- Example: Chapter 33, ECG #36

Atrial Fibrillation (AF)

Epidemiology and Clinical Characteristics

- AF is the most common sustained arrhythmia
  - The global prevalence of AF is approximately 33 million
  - 10% of persons over the age of 80 have AF
- The frequency increases with age and with the presence of cardiac disease especially
  - Mitral valve disease
  - CHD
  - Hypertension
  - Chronic pulmonary disease
  - Diabetes
  - Obesity
  - Chronic kidney disease
- Associated with marked increase in the risk of peripheral embolism and stroke
- An important risk factor for heart failure (HF) and death
- Pathologic and physiologic changes in the atria (especially the left atrium) associated with aging, hypertension, and the conditions listed above facilitate the development of AF
- AF may also occur in patients with hyperthyroidism, alcohol use, pulmonary infections, or exercise in susceptible individuals
- Exercise-related AF may be secondary to high catecholamine levels during exercise or during the period of high vagal tone following exercise
- AF occurs frequently following cardiac surgery
  - A randomized trial of rate versus rhythm control for post-operative AF demonstrated no significant difference in AF rates at 60-day follow-up. The aim of rhythm control post-operatively should be to ameliorate AF-related symptoms or hemodynamic sequelae. BB, amiodarone, and possibly statins may decrease the rate of occurrence
- Lone AF (AF in the absence of other heart disease) occurs in younger individuals (<60–65 years), is often influenced by genetic factors, and may be triggered by alcohol, sleep, and exercise
  - A family history of AF is present in up to 38% of individuals with lone AF
- Symptoms of AF may include palpitations, decreased exercise tolerance, dizziness, presyncope, syncope, dyspnea, pulmonary edema, and severe HF depending on coexisting comorbidities
- A significant proportion of patients are unaware of the arrhythmia, including older patients with hyperthyroidism (apathetic hyperthyroidism)
- The majority of patients with symptomatic AF also experience episodes of asymptomatic (silent) AF

- In the ASSERT trial, subclinical atrial tachyarrhythmias (episodes of atrial rate >190 beats per minute for more than 6 minutes), without clinical AF, occurred frequently (10.1%) in patients with hypertension and pacemakers (PPM) or implantable cardioverter defibrillators (ICD)s and were associated with a significantly increased risk of ischemic stroke or systemic embolism (HR adjusted for predictors of stroke 2.50; 95% CI, 1.28–4.89; $P = 0.008$) [3]

Electrocardiographic Features

- AF is characterized by the absence of organized atrial activity, associated with an irregularly irregular ventricular rhythm
- When atrial activity is visible (f waves), it is fast (>300 bpm) and irregular (variable f-f interval)
- The ventricular rate may be regular in cases of AV dissociation with junctional rhythm
  - Consider digoxin toxicity in this context
- The QRS is ordinarily narrow but it may wide (>120 ms) in cases of preexisting BBB, aberrant intraventricular conduction, or preexcitation
- Example: Chapter 33, ECG #38

Atrial Fibrillation Classification [4, 5]

- New-onset AF—First occurrence regardless of the duration or symptoms
- Paroxysmal AF—Recurrent AF (two or more episodes) that terminates spontaneously within 7 days
- Persistent AF—Continuous AF that persists beyond 7 days or AF of ≥48 hours but less than 7 days duration in which a decision is made to electrically or pharmacologically cardiovert
- Longstanding Persistent AF—Continuous AF of greater than 12 months duration
- Permanent AF—Continuous AF of greater than 12 months duration in patients in whom a decision has been made not to restore or maintain sinus by any intervention

Pathophysiology of AF

- Two mechanisms account for the majority of cases of atrial fibrillation
  - Foci in the pulmonary veins with very rapid rates initiate and maintain atrial fibrillation in many patients with paroxysmal AF
  - Multiple unstable and varying "wavelet" depolarization circuits, reentrant circuits, or rotors in both atria, resulting in fibrillatory conduction contribute to arrhythmia perpetuation, particularly in patients with persistent AF
- AF results in hemodynamic changes resulting from the lack of an appropriately-timed atrial contraction leading to less-efficient left ventricular filling and ejection
- Clinical effects
  - AF is often not perceived by normal subjects at rest, since the cardiac output can be maintained by increased contractility
  - Exercise tolerance and maximum cardiac output are compromised, leading to the dyspnea experienced by some patients
  - This becomes clinically important in cases of impaired LV diastolic function (aortic stenosis, left ventricular hypertrophy, hypertrophic cardiomyopathy), where atrial transport is important, as well as in patients with systolic HF and low reserve, where AF may cause decompensation and hospitalization
  - AF with fast ventricular rates may precipitate angina in patients with CHD and is particularly dangerous in patients with accessory atrioventricular pathways with short refractory periods where it may degenerate to VF

  - Fast rates may cause mechanical remodeling of the ventricles leading to LV systolic dysfunction and HF (tachycardia-induced cardiomyopathy)

- Structural and electrical remodeling of the atria resulting from prolonged AF promotes persistence of the arrhythmia

Treatment Considerations for AF

Cardioversion

- New onset AF may be an indication for urgent cardioversion, deferred cardioversion after three weeks of antithrombotic therapy, or rhythm control without cardioversion (see Electrical Cardioversion)
  - Cardioversion should be considered for all patients with new-onset AF in the absence of spontaneous conversion
- Major issues in the long-term treatment of atrial fibrillation are the choice of rhythm versus rate control strategies and antithrombotic therapy

Rate vs. Rhythm Control

- Rate control
  - Rate control is initial treatment for patients who do not require urgent cardioversion
  - Agents used for rate control include BB, non-dihydropyridine CCB (e.g. diltiazem and verapamil), and digoxin to control the ventricular rate to below 110 bpm at rest
  - Amiodarone can be used for rate control if other agents fail and is also useful to maintain sinus rhythm
  - BB (e.g. metoprolol, or esmolol for intravenous administration in the acute setting) are preferred in patients with CHD, especially in the presence of angina or acute coronary syndromes
  - CCB are used preferentially in patients with intolerance to BB
  - Digoxin may be used in patients with HF, but should only be used as chronic therapy together with BB
  - If pharmacotherapy is not effective in achieving ventricular rate control and the patient is not a candidate for rhythm control interventions, ablation of the AV node and implantation of a pacemaker may be considered as a treatment of last resort
- Rhythm Control
  - In patients with symptomatic AF and no structural heart disease, class IC agents are generally employed as first-line therapy
  - Amiodarone is more effective in maintaining sinus rhythm than Class IC antiarrhythmic agents (e.g. propafenone, flecainide) or sotalol (Class III) but is considerably more toxic than other agents and is generally reserved for elderly patients or as a last line agent in younger individuals
  - Dronedarone (an amiodarone analog with short half-life and no iodine moiety) appears to be less effective than amiodarone, is contraindicated in patients with HF, and requires monitoring of liver function tests due to risk for hepatic necrosis
  - Dofetilide (Class III) is less frequently used because of restricted access, proarrhythmia, and the requirement for continuous monitoring
  - Class IA antiarrhythmic agents (e.g. procainamide, disopyramide) are not commonly used, except occasionally in in patients with hypertrophic cardiomyopathy or vagally-mediated atrial fibrillation
  - BB are indicated for prevention of exercise-induced atrial fibrillation and are sometimes used before rhythm control therapy to control the ventricular rate
  - Class I antiarrhythmic drugs should always be used in conjunction with a BB (or a CCB if BB are not tolerated) to prevent the occurrence of class IC-induced atrial flutter with 1:1 AV conduction
  - Catheter ablation is an option as second line therapy for rhythm control in symptomatic patients who have failed at least one antiarrhythmic drug and in whom

additional trials of antiarrhythmic drugs are not preferred by the patient (see Catheter Ablation) [5]

- There is no evidence that survival is significantly different between rhythm and rate control strategies

Stroke Prevention

- The CHA_2DS_2-VASc score may be used to estimate the risk of stroke in patients with non-rheumatic AF [6]
  - The letters stand for **C**ongestive HF (1 point), **H**ypertension, **A**ge 75 and above (2 points), **A**ge 65–74 (1 point), **D**iabetes (1 point), $\mathbf{S}_2$ (history of peripheral embolism, stroke, or TIA) (2 points), **V**ascular disease (1 point), and **Sc** (sex category; female gender—1 point)
  - CHA2DS2-VASc stratifies patients with a tenfold range of annual risk of stroke ranging from 0.2% to 12.2% and has found wide application in estimating the advisability of antithrombotic therapy
  - Patients with a CHA2DS2-VASc score of 0 may be given ASA, those with a score of 1 may be given ASA or oral anticoagulation and those with a score of 2 should be given oral anticoagulation
- ASA is prescribed in doses of 75–325 mg
- Warfarin (goal INR 2–3) was historically used as the antithrombotic therapy of choice in the majority of patients
  - New antithrombotic agents have been approved for AF and are now supplanting warfarin
  - In addition to comparable or better efficacy, these agents:
    - Have predictable pharmacodynamics and do not require monitoring
    - All appear to be associated with a lower risk of intracranial hemorrhage compared with warfarin
    - All of these agents presently have clinically available antidotes to reverse the effects in the event of major bleeding
  - Dabigatran (a direct thrombin inhibitor), administered 150 mg twice daily for those age <75 years or with preserved renal function
    - For older patients or those with chronic kidney disease, a dose of 75 mg twice daily is recommended
    - Concern has been raised regarding excessive bleeding, and a higher rate of myocardial infarctions
  - Rivaroxaban (an orally-active direct factor Xa inhibitor), administered 20 mg once daily with the evening meal
    - Lower doses (15 mg daily) are recommended for those with renal failure (CrCl 15–50 mL/min)
  - Apixaban (an orally-active direct factor Xa inhibitor), administered 5 mg twice daily.
    - Lower doses (2.5 mg twice daily) are recommended for patients when two of the following three conditions are present: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL.
  - Edoxaban (an orally-active direct factor Xa inhibitor), administered 60mg once daily
    - Lower doses (15 or 30 mg daily) are recommended if any of the following are present: creatinine clearance of 30–50 ml/min, body weight ≤60 kg, concomitant use of verapamil, quinidine, or dronedarone
- In patients with a history a clinically significant bleeding on theraputic anticoagulation or who are deemed ineligible for therapeutic anticoagulation, left atrial apendage occlusion or exclusion may be considered.

Atrial Flutter (AFL)

- AFL is a reentrant arrhythmia similar to AF
  - As in AF, the SAN and AVN are not required for the initiation and maintenance of the arrhythmia
  - The difference between AF and AFL lies in the regularity of the atrial cycle length (F-F interval) in AFL, with a rate usually in the range of 250–320 bpm
  - Lower flutter rates are observed in the presence of antiarrhythmic agents (Class I, III) and in some patients with diseased atria
- The commonest form of AFL (Type I or typical AFL) is due to a single reentrant circuit circulating around the tricuspid annulus in the RA
- This circuit is most often counterclockwise in direction but may be clockwise in some individuals
  - AFL usually results in a ventricular rate of about 150 bpm, with an atrial rate of about 300 bpm and 2:1 AV nodal conduction
    - Other even AV conduction ratios (e.g. 4:1, 6:1) may also occur
    - Odd AV conduction ratios (e.g. 3:1, 5:1) are less common
    - Irregular ventricular response (usually with Wenckebach periodicity) may be seen in the presence of medications affecting the AV node (e.g. digoxin, beta blockers, calcium channel blockers) or in the presence of AV nodal disease
  - AFL with 1:1 AV conduction will result in very high ventricular rates
    - May be associated with wide QRS duration due to ventricular aberration
    - May cause hemodynamic instability
- The classical ECG has a saw tooth appearance (most visible in V1-2 or in the inferior leads)
  - This may not be present in patients with atypical (Type II) AFL, which has a different locations and reentrant circuits than typical AFL
- Transition between AFL and AF is commonly observed in patients with all types of AFL
- Vagal maneuvers, adenosine, or esmolol may be used to slow AV conduction and reveal the sawtooth F-wave pattern in cases of AFL with 2:1 conduction where the diagnosis may be in doubt
- Unlike AVNRT or AVRT that may break after these maneuvers or medications, AFL does not typically break in response to AV nodal blocking agents, as the AV node does not participate in the reentrant circuit

Typical (Type I) Atrial Flutter

- Typical (Type I) AFL results in a negative F wave in lead II and positive F wave in aVL and aVR
- The reentrant circuit in Type I AFL includes the cavotricuspid isthmus (located between the IVC, the ostium of the coronary sinus, and the tricuspid valve annulus)
  - Referred to as "isthmus dependent" and can be entrained (since there is an excitable time gap in the reentry loop) and ablated at the isthmus
  - Type I AFL may proceed in a counterclockwise (90% of the cases, positive F waves in V1) or clockwise (negative F waves in V1) fashion
- Example: Chapter 33, ECG #37

Atypical (Type II) Atrial Flutter

- Atypical (Type II) AFL results in faster atrial rates (340–440 bpm), and often cannot be entrained unless the stimulating catheter is in close proximity to the reentrant circuit

- Positive F waves may be observed in the inferior leads
- Activation of the atria at the fast rates may result in fibrillatory conduction (described in the AF section)
- The reentrant pathway may be located in either the RA or LA
- Type II AFL may be distinguished from coarse AF by the regularity of F waves
- While the majority of type I (typical/right-sided) flutters are isthmus-dependent, this occurs only in a minority of type II (atypical) cases

Atrioventricular Nodal Reentrant Tachycardia (AVNRT)

- AVNRT is a common supraventricular arrhythmia
- Usually manifested at a young age
- Most patients do not have structural heart disease
- Characterized by regular narrow QRS tachycardia at rates between 120 and 220 bpm with abrupt onset and offset
  - The AV node may be divided functionally into two pathways with different refractory periods and conduction velocities (fast and slow) which creates the substrate for AV node reentry
- AVNRT may be classified into typical, atypical, and intermediate subtypes

Typical (Slow-Fast) AVNRT

- Accounts for 90% of cases
- Antegrade conduction (toward the ventricles) proceeds through the slow pathway and retrograde activation through the fast pathway (Fig. 15-1a)
  - This causes rapid retrograde activation of the atria (P negative in II, III and aVF, positive in aVR) that is simultaneous with antegrade ventricular activation and, as a result, the P wave occurs at the within or at end of QRS complex (pseudo R prime)
  - The RP interval is shorter than half of the RR interval of the AVNRT (Short RP tachycardia)
- Example: Chapter 34, ECG #40

Atypical (Fast-Slow) AVNRT

- Activation occurs in the opposite direction to that of typical AVNRT
- Antegrade conduction is via the fast pathway and there is late activation of the atria from retrograde conduction via the slow pathway (Fig. 15-1b)
  - The P wave occurs late and within the ST segment in this long RP tachycardia

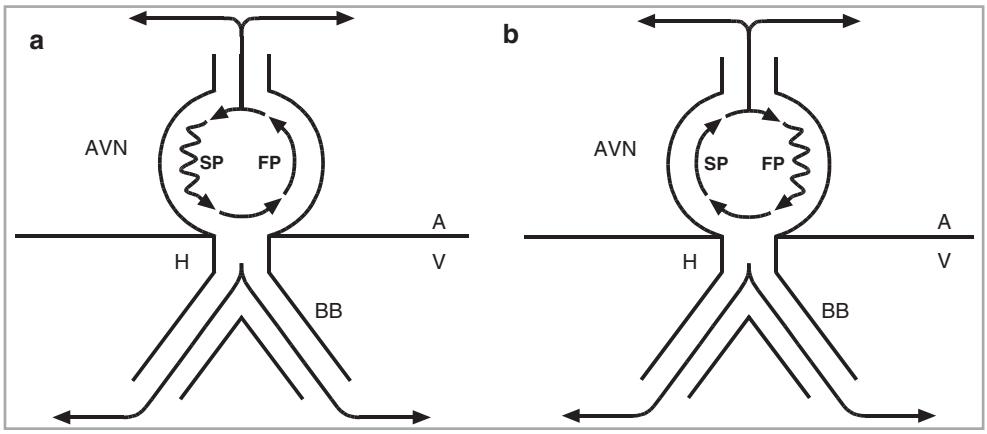

FIGURE 15-1

Schematic diagrams illustrating mechanisms of atrioventricular nodal reentrant tachycardias. (**a**) Typical (slow-fast) AVNRT. (**b**) Atypical (fast-slow) AVNRT (Modified from [7])

- AVNRT is usually precipitated by a premature beat (either atrial or ventricular) that is blocked in either the slow or fast pathway as a result of different refractory periods between the two pathways, creating the substrate for reentry
  - Usually APC in typical AVNRT
  - Either PVC or APC in atypical AVNRT

Atrioventricular Reentrant Tachycardia (AVRT)

- Atrioventricular reentrant tachycardias (AVRTs) are associated with the presence of accessory pathways that function as part of the tachycardia reentrant circuit
- A classical example is the Wolff-Parkinson-White (WPW) syndrome
  - The baseline electrocardiogram in classical WPW shows a short PR and wide QRS with a delta wave at the onset of the QRS and secondary T-wave changes (in the opposite direction to the QRS)
  - Atrial pacing at increasing rates results in widening of the QRS complex and magnifies the delta wave by prolonging the conduction time through the AV node and increasing the degree of manifest preexcitation (conduction via the accessory pathway)
- The macro-reentrant circuit between the atria and the ventricles involves conduction via an accessory pathway between the atria and ventricles (e.g. bundle of Kent), as well as the AV node
  - Orthodromic AVRT—conduction occurs antegrade through the AV node and retrograde via the accessory pathway, resulting in a narrow-complex tachycardia with retrograde P waves occurring after the QRS complex typically within the ST segment (Fig. 15-2a), Example: Chapter 33, ECG #41
  - Antidromic AVRT (less common)—conduction occurs antegrade through the accessory pathway and retrograde via the AV node, resulting in a wide-complex, short RP tachycardia (Fig. 15-2b and Chapter 33 ECG #42)
- In both orthodromic and antidromic AVRTs, the RP interval remains constant if the SVT rate changes, ST-T changes may be present, and the arrhythmia is initiated by an APC or PVC
- Arrhythmias related to a concealed accessory pathway (no delta wave on baseline ECG) conducting only in the retrograde direction manifest on the surface ECG as narrow QRS tachycardias with heart rates between 120 and 200 bpm
- In addition to the bundle of Kent, accessory pathways include
  - James fibers—intranodal or paranodal fibers that bypass all or part of the AV node to enter the bundle of His before the bifurcation, resulting in an electrocardiogram with a short PR with normal duration QRS (enhanced AV conduction may also result in the same electrocardiographic configuration)

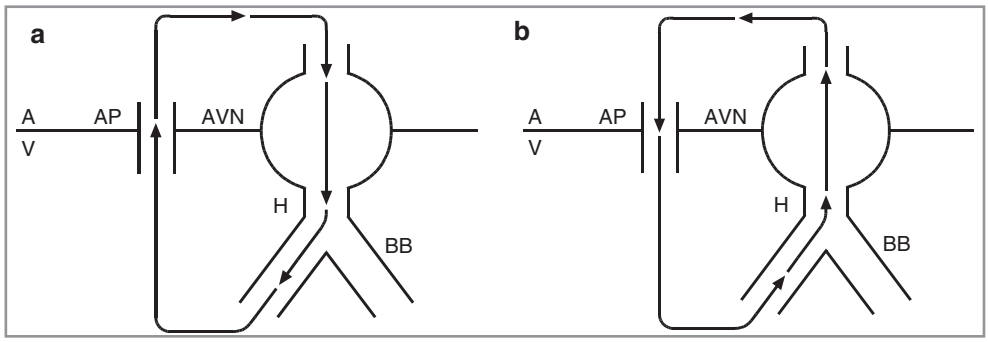

FIGURE 15-2

Schematic diagrams illustrating mechanisms of atrioventricular reentrant tachycardias. (**a**) Orthodromic AVRT. (**b**) Antidromic AVRT (Modified from [7])

- Lown-Ganong-Levine (LGL) syndrome is the occurrence an ECG with a short PR and normal duration QRS together with tachyarrhythmias
- Mahaim fibers are atriofascicular pathways that are typically associated with left bundle branch block (LBBB) tachycardias in which the atriofascicular fiber (typically RA to right bundle branch (RBB) connection) is used as the antegrade limb and the AV node as the retrograde limb of the reentrant circuit
- More rarely, nodoventricular and fasciculoventricular connections may be present
- In a small percentage of patients, multiple accessory pathways may coexist and other congenital anomalies may be present in association with preexcitation (e.g. hypertrophic cardiomyopathy, Ebstein's anomaly)

■ The development of atrial fibrillation in patients with accessory pathways (pre-excitation syndromes) is a serious event, since it can lead to very high ventricular rates and may degenerate to ventricular fibrillation (VF) and death in patients in whom one or more accessory pathways is associated with a short antegrade refractory period
■ Pre-excitation predisposes to atrial fibrillation (occurring in 10–20% of cases)

- The ECG demonstrates irregularly irregular RR intervals with wide QRS configuration (which may vary from beat to beat due variation in the degree of preexcitation)
- The ability of the accessory pathway to rapidly conduct during AF is an independent predictor of death in this context

  ■ Usually due to hemodynamic collapse and/or VF

■ Patients with preexcitation syndromes should be risk stratified with respect to the risk of sudden cardiac death (SCD)

- The incidence of SCD overall is rather low (1–2 per 1000 per years) [8]
- The majority of patients who suffer SCD experience recurrent AVRT before SCD, underscoring the importance of risk stratification and appropriate treatment in all patients with symptomatic arrhythmias associated with preexcitation
- Patients with symptomatic AVRT or AF, syncope, presyncope, and those with multiple accessory pathways should undergo catheter ablation (rare exceptions include patients who prefer pharmacological therapy with antiarrhythmic drugs to curative catheter ablation and those in whom catheter ablation is considered high risk because of proximity of the accessory pathway to the bundle of His)
- Electrophysiologic study (EPS) to evaluate prognosis in asymptomatic patients is generally not necessary unless there is family history of sudden death or the patient is engaged in high-risk professions (e.g. airline pilots) or competitive athletics
- Class IA antiarrhythmic agents (e.g. IV procainamide), amiodarone or cardioversion may be used to terminate the arrhythmia
- Verapamil and adenosine are contraindicated for termination of preexcited AF and digoxin is contraindicated in patients with preexcitation (may increase conduction via the accessory pathway and result in higher ventricular rates due to shortening of the accessory pathway refractory period)

Non-Paroxysmal Junctional Tachycardia (NPJT)

■ Uncommon tachycardia
■ Due to enhanced automaticity of a focus in the bundle of His
■ May develop following myocardial infarction, digoxin toxicity, myocarditis, or cardiac surgery
■ Retrograde P waves may be present
■ Permanent junctional reciprocating tachycardia (PJRT), typically found in the pediatric population, is rarely encountered in adults

TABLE 15-1

APPROACH TO THE NARROW COMPLEX TACHYCARDIA

- Evaluate regularity of the ventricular response
  - Irregularly irregular ventricular rate suggests AF or MAT
    In MAT there are distinct P waves of at least three configurations (and at least three each of PP, PR, and RR intervals)
- What is the atrial rate?
  - 100–150 beats/min suggests ST, IST, MAT, NPJT
  - 150–250 beats/min suggests AT, AVNRT, AVRT, PJRT
  - 250–350 beats/min suggests AFL
  - >350 beats/min suggests AF
- What is the P wave configuration?
  - In ST, IST and AT (when the focus is near the SA node) similar to sinus rhythm
  - Inverted in the inferior leads in AVNRT, AVRT with septal pathway, and typical flutter
- What is the RP interval?
  - Short (less than half of the RR interval) in orthodromic AVRT and the typical (slow-fast) AVNRT where the P wave has a retrograde configuration (e.g. negative in lead II, positive in aVR)
    Less commonly, a short RP tachycardia may be JT or AT with first-degree AV block
  - Long in cases of antidromic AVRT and atypical (fast-slow) AVNRT; may be long in AT with first degree AV block
- Response to vagal maneuvers or pharmacologic AV nodal blockade?
  - The atrial activity of AF and AFL may become apparent
  - AVNRT and AVRT may be terminated
  - Administration of adenosine, non-dihydropyridine CCB (diltiazem, verapamil) or beta blockers (esmolol, metoprolol) may have similar effects
    These techniques should not be performed in patients with AF and a history of preexcitation

DIFFERENTIAL DIAGNOSIS OF TACHYARRHYTHMIAS

A. **Narrow Complex Tachycardias (NCT),** Table 15-1
B. **Wide Complex Tachycardias (WCT; see also Chapter 23 Ventricular Arrhythmias and Defibrillators)**

- Although the great majority of NCT are supraventricular (VT may rarely be associated with a narrow QRS), wide QRS tachycardias may be either ventricular or supraventricular
  - Although several have been proposed, there is no criterion or combination of criteria that can correctly identify the arrhythmia in all cases [9, 10]
  - Many patients with WCT are hemodynamically unstable and require urgent therapy, possibly cardioversion
  - On the other hand, hemodynamic stability does not exclude VT as a cause of the arrhythmia
- See Chapter 23 for variables predicting VT and clinical assessment
- When the diagnosis remains unclear, it is prudent to treat the arrhythmia as ventricular rather than supraventricular

ELECTRICAL CARDIOVERSION

- Electrical cardioversion is useful in patients with sustained symptomatic atrial tachyarrhythmias
- Table 15-2 summarizes recommended uses of cardioversion in this context
- The risks of direct current cardioversion are mainly related to thromboembolism and arrhythmias such (bradycardia and ventricular tachyarrhythmias) as well as hypotension and other anesthesia-related complications
  - Patients with AF of unknown duration or lasting 48 h or longer should receive oral anticoagulation (warfarin INR 2.0 to 3.0 or therapeutic dose of direct oral anticoagulant) for at least 3 weeks prior to and 4 weeks after cardioversion

TABLE 15-2

USE OF CARDIOVERSION FOR MANAGEMENT OF SVT

RECOMMENDED	NOT RECOMMENDED
■ Indicated in all patients with SVT resulting in hemodynamic instability, pulmonary edema, angina, or acute myocardial infarction ■ Cardioversion is recommended as a Class I indication for atrial fibrillation [4]: – In the presence of preexcitation – In patients without hemodynamic instability, when symptoms of AF are unacceptable to the patient – With early relapse after cardioversion with antiarrhythmic drug or recent catheter ablation	■ Patients with frequent recurrences – Elimination of the underlying pathophysiologic mechanism and/or pharmacologic therapy aimed at prevention of recurrence ■ Patients with automatic supraventricular tachyarrhythmias including ST, IST, AT, NPJT, and MAT

- It is important to continue anticoagulation after cardioversion due to stunning of the left atrium and atrial appendage by cardioversion, which may increase the risk of thrombus formation and systemic embolism

- Transesophageal echocardiography (TEE) may be performed immediately prior to cardioversion to assure the absence of left atrial thrombus in patients who are not therapeutically anticoagulated prior to the procedure and in whom immediate cardioversion is deemed appropriate
  - Spontaneous echo contrast, or "smoke," is a marker of stasis and propensity to develop thrombi and may be related to fibrinogen-mediated erythrocyte aggregation
- Atrial arrhythmias that are reentrant in mechanism may be terminated by pacing and capturing the atria at a rate faster than that of the underlying arrhythmia
- Continuous atrial overdrive pacing (continuous electronic adjustment to pace the atrium at a rate slightly higher than the patient's intrinsic sinus rhythm, as a means of potentially preventing the initiation of atrial fibrillation) does not prevent the occurrence of atrial fibrillation (ASSERT trial)

CATHETER ABLATION

- Catheter ablation is commonly employed to treat patients with supraventricular tachyarrhythmias
  - Common SVTs subjected to catheter ablation are AFL, AT, AVRT and AVNRT
  - More recently, catheter ablation has been widely applied to the treatment of both paroxysmal and persistent AF
- Catheter ablation for SVT requires precise electrophysiologic mapping as well as operator and team experience
  - RF energy is typically used for most ablation procedures, although cryoablation is being used as an alternative to RF in selected patients
  - For AFL, AVRT, or AVNRT, success of catheter ablation depends on successful interruption of reentrant circuit
    - Typical AFL ablation is successful in >90% of cases and is achieved by ablation at the cavotricuspid isthmus
    - Atypical AFL is frequently successfully ablated but is more challenging than typical AFL and success rates are highly dependent on operator skill and experience
    - AVRT ablation depends on the successful mapping and ablation of the accessory pathway(s)
    - AVNRT ablation usually involves anatomically guided ablation of the slow AV nodal pathway

- Ablation procedures for AF
  - Surgical: typically done at the time of concomitant valvular or coronary bypass procedures
    - Maze
      - Various forms exist, but all include the creation of linear lines of block resulting in isolation of the pulmonary veins and an electrically compartmentalized atrium
      - Most maze procedures are currently performed with RF energy using a special clamping device but other energy sources such as cryo are also used by some operators
  - Catheter ablation for AF
    - Most common catheter ablation procedure and typically involves electrical "isolation" of the sites of arrhythmia origin using ablative energy to block electrical propagation, rather than the primary goal of ablating the site of origin
      - The pulmonary vein (PV) ostia are most often isolated based on the observation that paroxysmal AF is most often triggered by rapid firing from foci within the PVs
      - PV isolation may be achieved with the use of either radiofrequency (RF) or cryothermal ablation
      - Non-PV ablation sites (complex fractionated activity, posterior wall, mitral isthmus) or triggers (atrial tachyarrhythmias, premature atrial complexes) may be targeted at the time of catheter ablation. A randomized assessment of ablation strategy found no incremental benefit with additional linear ablation or ablation of complex fractionated electrograms at the time of index PV isolation for patients with persistent AF
      - However, there is agreement that mapping and ablation of non-PV triggers adds incremental benefit to PVI alone in patients in patients with both paroxysmal and persistent AF
      - Linear lesions may also be employed for the prevention or treatment of macroreentrant left atrial tachycardias/flutters in selected patients, particularly those undergoing repeat catheter ablation procedures
    - Indications for catheter ablation of AF include:
      - Symptomatic paroxysmal or persistent AF resistant to antiarrhythmic drug therapy
      - AF associated with hemodynamic compromise and resistant to antiarrhythmic drug therapy
      - A recent randomized controlled trial of catheter ablation versus antiarrhythmic drug therapy (CABANA) in patients with new-onset or untreated AF showed no significant difference in cardiovascular outcomes (including mortality and stroke) in an intention to treat analysis. A nonsignificant trend toward more favorable outcomes was observed in the ablation group and the trial was affected by a high crossover rate from the drug arm to catheter ablation
      - Evidence from randomized controlled trials supports the early use of catheter ablation in patients with AF and congestive heart failure [11]
      - Success rate for catheter ablation in patients with paroxysmal AF is 60–75% after first procedure and as high as 80–90% in subsequent procedures in the hands of skilled and experienced operators
      - Lower rate of success in persistent AF of greater than 6–12 months duration, marked left atrial enlargement, older patients, and in those with advanced structural heart disease
    - Anticoagulation after catheter ablation of AF
      - Following apparently successful catheter ablation of AF there is considerable debate regarding the safety of routine discontinuation of anticoagulation
      - Patients at high risk for stroke should generally receive long term anticoagulation regardless of the impact of catheter ablation on recurrent symptomatic AF

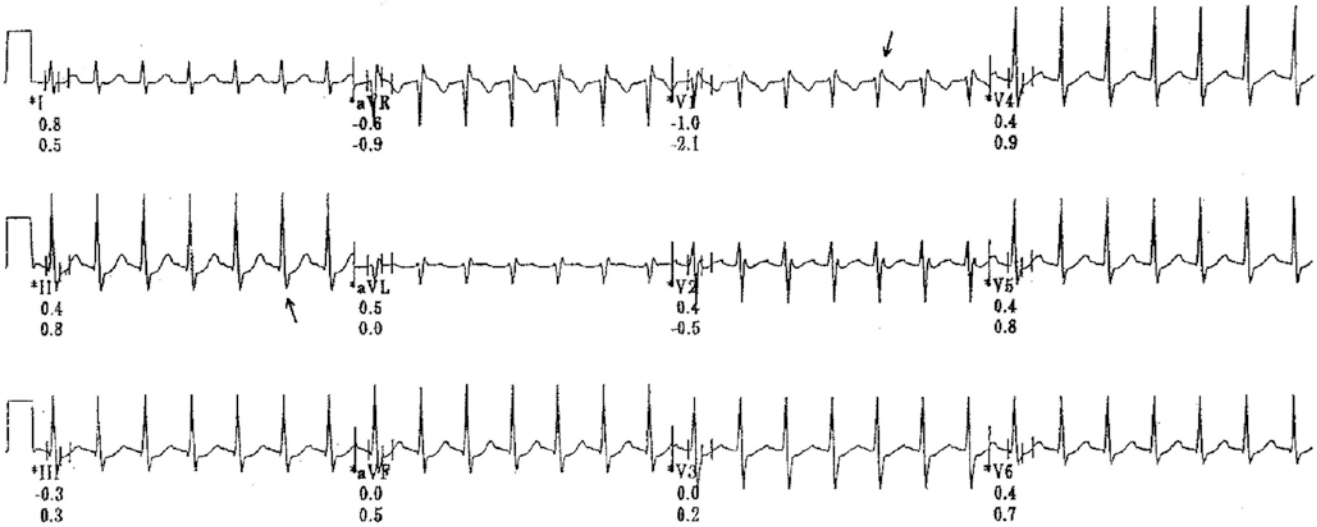

FIGURE 15-3

ECG for Question 1 (used with permission from [12])

- Ablation of atrial fibrillation is associated with a major complication rate of 3–6% including:
  - Thromboembolic stroke or TIA (0.5–1%)
  - Cardiac perforation with tamponade (1–2%)
  - Local catheter site or retroperitoneal bleeding (1%)
  - Phrenic nerve injury (more common with balloon vs. catheter technologies)
  - Atrio-esophageal fistula (<0.1%)
  - Pulmonary vein stenosis (<1%)
  - Peri-procedural death (<0.2%)

QUESTIONS AND ANSWERS

1. A 35-year-old woman presents to the ED because of sudden onset of palpitations. She has no history of cardiovascular disease and an ECG was normal one year ago during pregnancy. Her pulse is 160 bpm and regular, blood pressure is 110/60. Physical examination is within normal limits. Vagal maneuvers have no effect. The ECG reveals a regular, narrow-complex tachycardia at 160 bpm (Fig. 15-3). No P-waves can be seen in any lead. What is the most likely diagnosis?
   A. Sinus tachycardia
   B. Atypical AVNRT
   C. Typical AVNRT
   D. Antidromic AVRT
   E. Atrial flutter

   1. Answer: C. The sudden onset of the arrhythmia and the absence of physical findings related to increased sympathetic tone (e.g. fever) argue against sinus tachycardia. Atrial flutter would demonstrate regular F waves (at this rate, likely with 2:1 conduction). Among the remaining choices, typical AVNRT is the most common. Atypical AVNRT would have a long RP interval and P waves would likely be seen. Typical AVNRT will usually have P waves that are either hidden within the QRS complex (i.e. not visible) or attached to the terminal portion of the QRS complex. AVRT always exhibits P waves that occur after the QRS complex, usually in the ST segment.

2. What is the best initial treatment for the patient described in Question 1?
   A. IV amiodarone
   B. IV digoxin
   C. IV adenosine
   D. IV procainamide
   E. DC cardioversion

   2. Answer: C. Reentrant supraventricular tachyarrhythmias that include the AV node in the reentrant pathway are almost always interrupted with AV nodal-blocking agents, particularly adenosine. These include adenosine, beta-blockers (e.g. IV esmolol and metoprolol), non-dihydropyridine calcium channel blockers (e.g. IV diltiazem), and digoxin. Although digoxin may terminate this arrhythmia, it has a far slower onset of action and lower efficacy than the other agents listed. In addition, digoxin alone is not indicated for prevention of this arrhythmia (without concomitant use of beta blockers). Amiodarone is a multichannel antiarrhythmic and may terminate this arrhythmia, but it would take far longer than adenosine. Procainamide is a class IA antiarrhythmic that is typically used to terminate wide-complex tachycardias involving an accessory pathway or ventricular tachycardias that are hemodynamically well

tolerated. DC cardioversion would likely terminate this arrhythmia, but there is no indication for its use, given that the patient is hemodynamically stable.

3. A 78-year-old man with hypertension on amlodipine and irbesartan, DM on metformin, and hypercholesterolemia on atorvastatin, presents with a 1–2 week history of exertional dyspnea. He has no chest pain or fever. His blood pressure is 160/70 and his heart rate is 110 bpm, with an irregularly irregular pulse. Cardiac auscultation reveals no murmurs or extra heart sounds. Physical examination is otherwise normal. What diagnostic tests would be appropriate?
   A. Transthoracic echocardiogram
   B. Pulmonary function tests
   C. 12-lead electrocardiogram
   D. Thyroid function tests
   E. A and B
   F. A and C
   G. A, B, C
   H. A, C, D
   I. A, B, C, D

   3. Answer: H. The first appropriate test would be a 12-lead electrocardiogram to confirm the diagnosis of atrial fibrillation and to exclude an acute myocardial infarction or ongoing ischemia. Thyroid function testing should be performed for newly-diagnosed atrial fibrillation unless there is a clear alternative etiology (e.g. mitral stenosis, systemic infection, alcohol use). In this patient, a transthoracic echocardiogram would also be useful to ascertain whether there is left ventricular systolic or, more likely, diastolic dysfunction, or any significant valvular disease. In these situations, effective left atrial contraction is necessary for optimal left ventricular filling and, in the presence of atrial fibrillation, may cause early heart failure. Furthermore, the safety and selection of antiarrhythmic drugs is determined largely by the presence or absence of underlying structural heart disease.

4. What are the important therapeutic considerations for the patient described in Question 3?
   A. Immediate DC cardioversion
   B. DC cardioversion after 3–4 weeks of therapeutic anticoagulation
   C. Radiofrequency ablation
   D. Long-term therapeutic anticoagulation
   E. A and D
   F. B and D

   4. Answer: F. The patient is hemodynamically stable and is in no acute distress, therefore immediate DC cardioversion is not indicated. After effective rate control therapy is initiated with either a BB or CCB, DC cardioversion following at least 3 weeks of therapeutic anticoagulation is appropriate. Following cardioversion, anticoagulation should be continued for at least 4 weeks in all patients, to reduce the risk of thromboembolic events. In this patient, given the patient's age, hypertension, and diabetes, his CHA_2DS_2-VASc score is at least four, suggesting that long-term therapeutic anticoagulation would be indicated [13].

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CHAPTER 16

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Bradycardia and Pacemakers/CRT

CHAPTER OUTLINE

ABBREVIATIONS

ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
AV	Atrioventricular
BPEG	British Pacing Electrophysiology Group
bpm	Beats per minute
CHB	Complete heart block
CRT	Cardiac resynchronization therapy
CL	Cycle length
cSNRT	Corrected sinoatrial node recovery time
ECG	Electrocardiogram
EP	Electrophysiologic
FDA	Food and Drug Administration
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HR	Heart rate
HRS	Heart Rhythm Society
ICD	Implantable cardioverter defibrillator
LAFB	Left anterior fascicular block
LBBB	Left bundle branch block
LPFB	Left posterior fascicular block
LQT1	Long QT syndrome type 1
LV	Left ventricular
LVEF	Left ventricular Ejection fraction
MI	Myocardial infarction
NASPE	North American Society for Pacing and Electrophysiology
NYHA	New York Heart Association
PPM	Permanent pacemakers
RA	Right atrium
RV	Right ventricle
RBBB	Right bundle branch block
SA	Sinoatrial

SACT	Sinoatrial conduction time
SND	Sinus node dysfunction
SNRT	Sinoatrial node recovery time
VT	Ventricular tachycardia

DISORDERS OF IMPULSE GENERATION

Sinus Arrhythmia

- **Definition**: Phasic change in heart rate (HR) due to normal respiration
- **Pathophysiology**: Thought to be due to reflex inhibition of vagal nerve tone during inspiration—leading to *increase in HR during inspiration* and slowing during respiration—thought to help improve and synchronize alveolar gas exchange [1]
  - Normal sinus arrhythmia
    - Most pronounced in the young
    - May be associated with sinus pauses for ≥2 s
  - Abolishment of sinus arrhythmia
    - Can be achieved through parasympathetic blockade by atropine
    - Autonomic denervation after cardiac transplant
    - Depression of respiratory sinus arrhythmia after MI is associated with an increased risk of sudden cardiac death [2]
  - Non-respiratory sinus arrhythmia [3]
    - In contrast to sinus arrhythmia, non-respiratory sinus arrhythmia is the change of p-p intervals varying at random
    - May be seen in elderly individuals, or reflect digitalis toxicity, intracranial hemorrhage, or ischemic heart disease
- **Treatment**: respiratory sinus arrhythmia is usually not pathologic, even when associated with sinus pauses. When sinus arrhythmia coexists with symptomatic atrial tachyarrhythmias—as sometimes occurs in the case of young athletes—detraining with resultant de-conditioning may resolve the issue.

Sinus Bradycardia

- **Definition**: Defined as sinus node impulse rate ≤60 beats per min (bpm)
- **Pathophysiology**: Sinus bradycardia or sinus pauses rarely cause hemodynamic instability, except when associated with extracardiac disturbance. For example:
  - Increased vagal tone in the context of:
    - Nausea and vomiting
    - Bowel obstruction
    - Urinary retention
    - Intracranial mass
    - ***Special case***: *Carotid sinus hypersensitivity*
      - Sometimes considered a variant of vasovagal syncope, occurs more frequently in elderly patients and manifests as profound sinus bradycardia with sinus pauses from pressure on the carotid sinus
      - Dual-chamber pacing indicated for patients in whom recurrent syncope is caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure induces *ventricular asystole* lasting ≥3 s present (Class I recommendation; see further details) [4]

- Sinus bradycardia can be exaggerated through parasympathomimetic or sympatholytic effect of drugs, notably:
  - β-blockers and calcium-channel blockers
  - Digoxin
- **Treatment**: Identification of underlying etiology and avoidance of culprit agents is first-line treatment.
  - Minimally symptomatic sinus bradycardia with HR less than 40 bpm while awake is Class IIb indication for PPM [4].

Sinus Node Dysfunction (SND)

- **Definition**: First described as *sick sinus syndrome* by Ferrer in 1968 [5], SND subsumes a constellation of abnormalities of the sinus node and surrounding atrial tissue characterized by sinus arrest, inappropriate sinus bradycardia (in the absence of drugs), and chronotropic incompetence. It is often coupled with the concurrent rise of subsidiary pacemakers leading to coexisting atrial tachyarrhythmias (hence, the term *tachycardia-bradycardia syndrome*).
  - Typically diagnosed in seventh and eight decades of life
  - Median annual incidence of complete AV block is 0.6% with a prevalence of 2.1%, suggestive of concurrent specialized conduction system degeneration [6]
- **Pathophysiology**: Most commonly driven by senescence, SND may occur at any age due to destruction of sinus node cells through infiltration, collagen vascular disease, trauma, ischemia, infection or idiopathic degeneration [7]. Drugs can often exacerbate underlying SND (see Table 16-1).
- Predominant clinical manifestations of SND include:
  - Frequent sinus pauses, sinus arrest, or sinus exit block
  - Inappropriate and severe sinus bradycardia with chronotropic incompetence
  - Episodes of bradycardia alternating with atrial tachyarrhythmias (usually atrial fibrillation (AF), although may be other supraventricular arrhythmias)
  - AF with a slow ventricular response or with very slow recovery after spontaneous conversion or cardioversion to sinus rhythm

TABLE 16-1

CARDIOACTIVE DRUGS THAT MAY INDUCE OR WORSEN SINUS NODE DYSFUNCTION

B Blockers
Calcium channel blockers (e.g., verapamil, diltiazem)
Sympatholytic antihypertensives (e.g., α-methyldopa, clonidine, guanabenz, reserpine)
Cimetidine
Lithium
Phenothiazines (rarely)
Antihistamines
Antidepressants
Antiarrhythmic agents May cause sinus node dysfunction (SND) in normal subjects: amiodarone Frequently worsens *mild* SND: flecainide, propafenone, sotalol Infrequently worsens *mild* SND: digitalis, quinidine, procainamide, disopyramide, moricizine Rarely worsens *mild* SND: lidocaine, phenytoin, mexiletine, tocainide
Opiod blockers

Adapted from Cardiac Arrhythmia by Podrid and Kowey (Lippincott Williams and Wilkins, Philadelphia 2001) [8]

- **Diagnosis**: Usually made by clinical history of presyncopal symptoms or palpitations and confirmation on electrocardiogram (ECG). Other options include
  - Ambulatory ECG monitoring
  - Exercise testing to evaluate chronotropic competence
  - Electrophysiologic (EP) study may be diagnostic, and there is a class I indication to pursue EP study in patients with symptomatic bradycardia in whom a causal relationship between SND and symptoms has not been established [9]. Criteria evaluated include:
    - *Sinoatrial node recovery time (SNRT)*: SA node is overdrive suppressed with atrial pacing, and the time from last paced atrial beat to the first spontaneous sinus beat is measured. Centers differ on normal SNRT, although <1500 ms is conventional. A corrected SNRT (cSNRT) is the SNRT minus the sinus cycle length (CL), and is typically <550 ms
    - *Sinoatrial conduction time (SACT)*: is the time required for the sinus impulse to capture the atrium. Typically it is between 50 and 115 ms, and is often prolonged during SA block
- **Treatment**: Largely depends on the diagnosis of symptomatic bradycardia, for which the only effective treatment is permanent cardiac pacing. Guideline recommendations are presented below [4]
  - ***Class I indications*** for permanent pacing in SND:
    - SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms
    - Symptomatic chronotropic incompetence
    - Symptomatic sinus bradycardia from required drug therapy for medical conditions
  - ***Class II indications*** for permanent pacing in SND:
    - Symptomatic bradycardia with HR <40 bpm, although without documentation of level bradycardia (class IIa)
    - Syncope of unexplained origin with abnormal EP study (class IIa)
    - HR <40 bpm while awake with minimal symptoms (class IIb)

DISORDERS OF IMPULSE PROPAGATION

Disorders of impulse propagation: may occur at any point in the conduction system. Importantly, conduction block is distinct from the normal physiologic phenomenon of *interference*, in which a preceding impulse causes a period of refractoriness due to inactivation of ion channels.

Sinoatrial Exit Block

- **Definition**: also called SA exit block, it manifests as sinus arrest of variable length on surface ECG. Prevalence is 1% in otherwise normal subjects [10].
- **Pathophysiology**: defect of impulse propagation within the SA node
  - First-degree SA exit block cannot be detected on surface ECG because sinus node depolarization is not inscribed separately from atrial depolarization (i.e., the *p* wave)
  - Second-degree SA exit block
    - Type 1: progressive prolongation of conduction block within the sinus node until complete exit block occurs (surface ECG demonstrates progressive shortening of *p* – *p* intervals before block)
    - Type 2: spontaneous block of sinus impulse leading to sinus pause which is an *exact multiple* of the preceding *p* – *p* interval

- Third degree SA exit block: simply manifests as sinus arrest, usually with eventual appearance of subsidiary pacemaker (i.e., junctional escape rhythm)

■ **Treatment**: Sinoatrial exit block is usually treated in the context of SND, as indicated above

Atrioventricular (AV) Block

■ **Definition**: By convention, first-degree 'block' refers to impulses that are delayed, second-degree block refers to intermittent block of impulse conduction, and third-degree to complete block. Further specific terminology is described below.

- First-degree AV block is defined as PR interval >0.20 s; generally due to block at the level of the AV node, although when associated with bundle branch block, may occur more distal in the His-Purkinje system. Prevalence is 0.65% in healthy adults [11]. Largely benign by itself, recent data from the Framingham cohort suggest that PR prolongation may be associated with increased risks for AF, pacemaker implantation, and all-cause mortality over time [12]
- Second-degree AV block was first classified into two types by Mobitz in 1924
  - ■ Mobitz Type 1 (Wenkebach) AV block: characterized by progressive prolongation of the PR interval before non-conduction. Also generally associated with block at the level of the AV node.
    - Progressive shortening of *R–R* intervals prior to a dropped beat; shorter PR interval immediately after dropped beat
    - Irrespective of QRS width, usually represents an appropriate physiologic response to increasing HR through decremental conduction in the AV node
  - ■ Mobitz Type 2: characterized by sudden non-conduction of atrial impulse without change in preceding PR interval. Usually represents infranodal disease and as such is accompanied by wider QRS compared to Mobitz I.
    - Care should be taken to differentiate Mobitz II from a premature atrial complex (examine preceding *p–p* intervals) which causes physiologic interference and not conduction block
    - Some authors refer to multiple consecutive non-conducted impulses as 'high-degree' or 'advanced' heart block prior to true third-degree AV block
    - In the setting of AF, a prolonged pause ≥5 s is suggestive of underlying advanced second-degree AV block
  - ■ 2:1 AV block: characterized by sudden non-conduction of atrial impulse without change in preceding PR interval after a single QRS complex. Based on surface ECG, it is not possible to discern whether the location of 2:1 block is within the AV node or below the level of the node (i.e., infrahisian). In patients with 2:1 AV block, evaluation of contemporaneous conduction disturbances (e.g., Wenkebach-type Mobitz 1) is used to help infer level of block (see Fig. 16-1)
- Third-degree AV block, or complete heart block, occurs with absence of atrial impulse propagation to the ventricles and may manifest as ventricular standstill in the absence of an escape rhythm. When reversible etiologies are present (e.g., electrolyte disturbance, non-anterior ischemia, Lyme disease), temporary pacing is usually indicated

■ **Pathophysiology**: There are numerous potential etiologies for AV block.

- Physiologic AV block (first-degree of second-degree Type 1) is commonly due to enhanced vagal tone.
- Idiopathic fibrosclerosis of the conduction system (i.e., Lev's disease affecting the old and Lenegre's affecting the young),

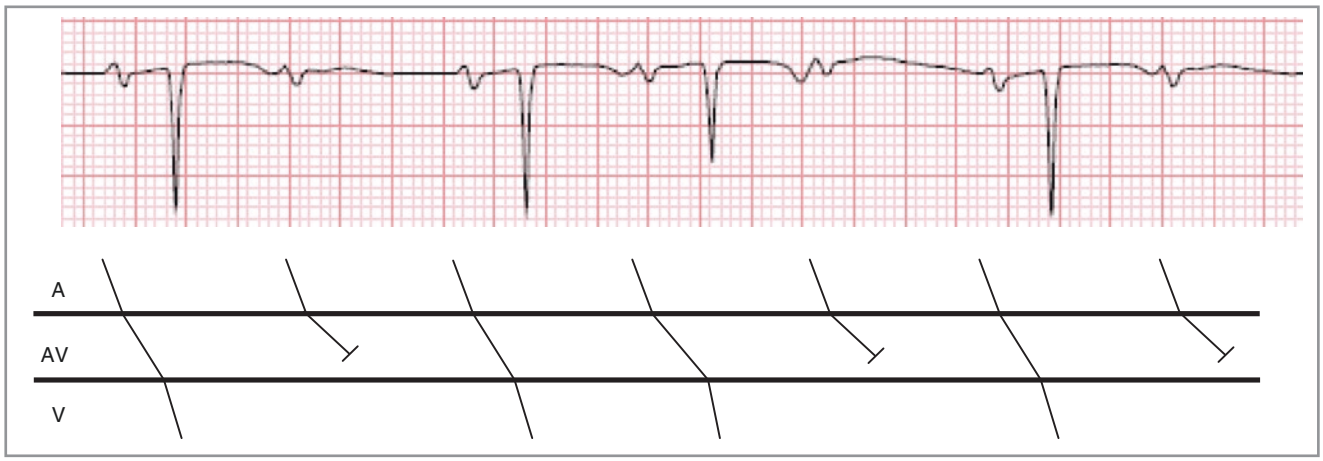

FIGURE 16-1

Ladder diagram of 2:1 AV block and Wenkebach type block. The rhythm strip shows a 2:1 block followed by short-stretch of Wenkebach and followed again with 2:1 block. The location of the block is inferred to be in the AV node due to the presence of Wenkebach, although cannot be determined conclusively without further information

- Infiltrative cardiomyopathy such as amyloidosis or sarcoidosis.
- Peri-AV nodal inflammation
  - Lyme disease
  - Myocarditis
  - Systemic lupus erythematosus
  - Dermatomyositis
- Endocrinologic states
  - Thyroid storm or myxedema
- Severe electrolyte disturbance
  - Hyperkalemia
- Drug toxicity or overdose, particularly when agents are added in combination or if either renal or liver insufficiency occurs, which leads to accumulation of the drugs.
  - β blockers
  - Calcium channel blockers
  - Amiodarone
  - Digoxin
- Iatrogenic etiologies of AV block are becoming increasingly common
  - Surgical or transcatheter aortic valve replacement
  - Alcohol septal ablation for hypertrophic cardiomyopathy
  - Transcatheter closure of ventricular septal defects
  - Complication of ablation during EP procedures.
- Congenital etiologies are other rare but predictable causes of AV block:
  - Familial AV conduction block
  - Sequela of neonatal lupus syndrome (particularly in babies born of mothers that are positive for antinuclear antibodies SSA/Ro and SSB/La)
  - Hereditary neuromuscular diseases such as myotonic dystrophy

TABLE 16-2

ACC/AHA/HRS CLASS I RECOMMENDATIONS FOR PERMANENT PACING

Recommendations in acquired atrioventricular block in adults
Third-degree and advanced second-degree AV block at any anatomic level associated with bradycardia and symptoms (including heart failure) or ventricular arrhythmias presumed to be due to AV block
Third-degree and advanced second-degree AV block at any anatomic level associated with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia
Third-degree and advanced second-degree AV block at any anatomic level in awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 s or any escape rate less than 40 bpm, or with an escape rhythm that is below the AV node
Third-degree and advanced second-degree AV block at any anatomic level in awake, symptom-free patients with AF and bradycardia with 1 or more pauses of at least 5 s or longer
Third-degree and advanced second-degree AV block at any anatomic level after catheter ablation of the AV junction
Third-degree and advanced second-degree AV block at any anatomic level with postoperative AV block that is not expected to resolve after cardiac surgery
Third-degree and advanced second-degree AV block at any anatomic level associated with neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms
Second-degree AV block with associated symptomatic bradycardia regardless of type or site of block
Asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 bpm or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node
Second- or third-degree AV block during exercise in the absence of myocardial ischemia
Recommendations in chronic bifascicular block
Advanced second-degree AV block or intermittent third-degree AV block
Type II second-degree AV block
Alternating bundle-branch block

SND sinus node dysfunction, *AV* atrioventricular, *SVT* supraventricular tachycardia, *VT* ventricular tachycardia, *MI* myocardial infarction

Adapted from the "2008 ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities." JACC 2008; 51: e1-e62 (4)

  - Myocardial ischemia is an important cause of AV and infranodal block
    - Many forms of AV block commonly seen in acute inferior MI, most often due to increased vagal tone, rarely due to AV nodal infarction
    - AV block and infranodal block due to acute anterior wall MI most often due to infarction of the conduction system

- **Treatment**: the initial course of treatment is to identify and remove any potential reversible offending agents. The decision for permanent pacing is often left to the discretion of the cardiologist, based on an appreciation of the relative stability of the underlying rhythm and the risk associated with developing symptoms. Class I indications are as outlined in Table 16-2

Intraventricular Block

- **Definition**: Failure in normal ventricular activation due to block in the His-Purkinje system.
  - The left and right bundle branches are commonly divided into a trifascicular system, consisting of the right bundle branch and the left anterior and posterior fascicles [13].

Although a septal fascicle has also been identified in anatomic studies, ECG manifestations of septal conduction block are debated and remain to be defined [14].

- Beyond commonly recognized right and left bundle branch blocks (RBBB and LBBB), other commonly used terminology for intraventricular block include:
  - Bifascicular block: Block is present when either the left anterior or left posterior fascicular block (LAFB or LPFB, but not both) is associated with RBBB
    - Most often precedes third-degree AV block, although rate of progression is variable and often slow [15]
  - Trifascicular block: Evidence of disease of all three fascicles present on success ECG tracings.
    - Typically manifests as *alternating BBB*. For example, RBBB + LAFB may be seen to alternate with RBBB + LPFB
    - Care should be made to contrast true trifascicular block from patients who demonstrate first-degree AV block in association with bifascicular block. This does *not* constitute evidence of trifascicular disease. When symptomatic, however, bifascicular AV block and *advanced AV block* (second-degree AV block with multiple non-conducted beats) is associated with increased mortality
- **Pathophysiology**: Intraventricular block may be due to a broad array of etiologies, similar to what was described above as causes of atrioventricular block. The special case of intraventricular block in the setting of MI deserves special mention
  - Inferior MI: usually associated with varying degrees of AV block from AV nodal artery ischemia or enhanced vagal tone from exaggeration of the Bezold-Jarisch reflex, *infranodal block is uncommon*
  - Anterior MI: can be associated with ischemia of the fascicles directly leading to true intraventricular block. In the pre-thrombolytic era, new fascicular or bundle branch blocks were common after an MI and were associated with a significantly increased risk of mortality [16]. Development of new bifascicular block after anterior MI is a Class I indication for pacing.
    - A simple scoring model characterizing the risk of progression to complete heart block after MI was developed by Lamas based on ECG criteria [17].
      - The complete heart block (CHB) scoring model assigned one point to the presence of well-recognized conduction disturbances, including: first-degree AV block, second-degree block (both type I and type II), LAFB and LPFB, RBBB, or LBBB. The risk of CHB after MI was linearly correlated with the total score (or simply, the sum of number of conduction disturbances) found on their presenting ECG. For example, a patient who's ECG after MI demonstrated 1st degree AV block and right bundle branch block would have a score of 2.
      - According to Lamas' study, patients with a CHB risk score of 0 had a 1.2% chance of developing complete heart block. CHB score of 1 was associated with 7.8% risk, 2 with 25% risk, and a CHB score of 3 or higher was associated 36% risk.
- **Treatment**: Permanent pacing is considered first-line in the treatment of bifascicular block with evidence for concurrent advanced AV node block or intermittent trifascicular block (see Table 16-2).
  - Treatment of intraventricular block in the setting of symptomatic left ventricular dysfunction is a special case which will be discussed further below in the cardiac resynchronization therapy section
  - Because of the relatively common incidence of bradycardia after MI (as indicated above based on the CHB score model), the American College of Cardiology (ACC)/American Heart Association (AHA) have clear guidelines on intervention, including the use of temporary pacing, for AV and intraventricular disturbance post MI (see Table 16-3)

TABLE 16-3

ACC/AHA GUIDELINES FOR TREATMENT OF ATRIOVENTRICULAR AND INTRAVENTRICULAR CONDUCTION DISTURBANCES DURING STEMI[A] AND ACC/AHA/HRS RECOMMENDATIONS FOR POST-MI PERMANENT PACING

Application of transcutaneous patches and standby transcutaneous pacing
Class I
Normal AV conduction *or* first-degree AV block *or* Mobitz type I second-degree AV block with new bundle branch block
Normal AV conduction *or* first-degree AV block *or* Mobitz type I second-degree AV block with fascicular block + RBBB
First-degree AV block with old or new fascicular block (LAFB or LPFB) *in anterior MI only*
First-degree AV block *or* Mobitz type I *or* type II second-degree AV block with old bundle branch block
Mobitz type I *or* type II second-degree AV block with normal intraventricular conduction
Mobitz type I *or* type II second-degree AV block with old or new fascicular block (LAFB or LPFB)
Class IIa
First-degree AV block with old or new fascicular block (LAFB or LPFB) *in non-anterior MI only*
Class IIb
Alternating left and right bundle branch block
Normal AV conduction with old bundle branch block
Normal AV conduction with new fascicular block (LAFB or LPFB)
First-degree AV block with normal intraventricular conduction
Mobitz type II second-degree AV block with new bundle branch block
Mobitz type II second-degree AV block with fascicular block + RBBB
Class III
Normal AV conduction with normal intraventricular conduction
Temporary transvenous pacing
Class I
Alternating left and right bundle branch block
Mobitz type II second-degree AV block with new bundle branch block
Mobitz type II second-degree AV block with fascicular block + RBBB
Class IIa
First-degree AV block *or* Mobitz type I second-degree AV block with new bundle branch block
First-degree AV block *or* Mobitz type I second-degree AV block with fascicular block + RBBB
Mobitz type II second-degree AV block with old bundle branch block
Mobitz type II second-degree AV block with normal intraventricular conduction
Mobitz type II second-degree AV block with old or new fascicular block (LAFB or LPFB) *in anterior MI only*
Class IIb
Normal AV conduction with new bundle branch block
Normal AV conduction with fascicular block + RBBB
Mobitz type I *or* type II second-degree AV block with old bundle branch block
Mobitz type II second-degree AV block with old or new fascicular block (LAFB or LPFB) *in nonanterior MI only*
Class III
Normal AV conduction *or* first-degree AV block *or* Mobitz type I second-degree AV block with normal intraventricular conduction
Normal AV conduction *or* first-degree AV block *or* Mobitz type I second-degree AV block with old or new fascicular block (LAFB or LPFB)
Normal AV conduction with old bundle branch block

TABLE 16-3

(CONTINUED)

Class I recommendations for permanent pacing after the acute phase of myocardial infarction
Persistent second-degree AV block in the His-Purkinje system with alternating bundle-branch block or third-degree AV block within or below the His-Purkinje system after ST-segment elevation MI
Transient advanced second- or third-degree infranodal AV block and associated bundle-branch block. If the site of block is uncertain, an electrophysiological study may be necessary
Persistent and symptomatic second- or third-degree AV block

Adapted from the "2004 ACC/AHA Myocardial Infarction." Circulation 2004; 110: e82-e293 [18], and the "2008 ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities." JACC 2008; 51: e1-e62 (4)

AV, atrioventricular; BBB, bundle branch block; BP, blood pressure; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; MI, myocardial infarction; RBBB, right bundle branch block

[a]Except where specified, all indications include anterior *and* nonanterior MI

PERMANENT PACING

PPM utilize placement of pacing electrodes within (or to the epicardial surface of) the heart attached to a pulse generator.

- Modern options in PPM selection include single-chamber atrial pacemaker (rarely used), single-chamber ventricular pacemaker, and dual-chamber pacemakers.
- Selection of device is driven by indication for pacing (usually SND or AV block) and whether or not there is a desire (or substrate) for rate responsiveness.
- As devices have become more sophisticated, the nomenclature used to define PPM functionality has been updated. A brief review is provided below

Coding/Nomenclature

- **Background**: The first coding system for PPM was proposed in 1974 [19] and was jointly updated by the North American Society for Pacing and Electrophysiology (NASPE) and British Pacing Electrophysiology Group (BPEG) in 2002 [20].
- The combined NASPE/BPEG generic code, or NBG code, outlines five distinct positions to describe PPM activity (see Fig. 16-2).
- **Commonly used codes**:
  - VVI or VVIR: also called "ventricular demand pacing"—this code is used in single-chamber ventricular lead devices in which the ventricle is paced, sensed, and inhibited in response to a sensed beat. It is commonly employed in patients with chronic atrial fibrillation and slow ventricular response. Two important caveats:
    - AV synchrony is not maintained in VVIR mode, and chronic right ventricular pacing is associated with an increased risk of heart failure (HF) hospitalization and AF due to increased ventricular dyssynchrony [21, 22]
    - In addition, some patients with chronic VVI pacing develop the pacemaker syndrome. Similar to what is seen in complete heart block, patients manifest a reduction in stroke volume, and may also demonstrate atrial contraction against a closed tricuspid or mitral valve. Reported symptoms include weakness, lightheadedness, a sensation of throat fullness, palpitations, near syncope and syncope
  - DDD or DDDR: represents dual-chamber pacing which is the most "physiologic." Requiring the use of an atrial and ventricular lead, the PPM is typically programmed

The Revised NASPE/BPEG Generic Code for Antibradycardia Pacing

Position:	I	II	III	IV	V
Category:	**Chamber(s) Paced**	**Chamber(s) Sensed**	**Response to Sensing**	**Rate Modulation**	**Multisite Pacing**
	O = None **A** = Atrium **V** = Ventricle **D** = Dual (A + V)	**O** = None **A** = Atrium **V** = Ventricle **D** = Dual (A + V)	**O** = None **T** = Triggered **I** = Inhibited **D** = Dual (T + I)	**O** = None **R** = Rate modulation	**O** = None **A** = Atrium **V** = Ventricle **D** = Dual (A + V)
Manufactures' designation only:	**S** = Single (A or V)	**S** = Single (A or V)			

FIGURE 16-2

The revised NBG coding system. From: "The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group." Pacing Clin Electrophysiol 2002; 25: 260-64 (19)

to maximize appropriately timed and intact native A-V conduction (i.e., through self-inhibition), add ventricular paced beats in the presence of significant AV delay or block (after allowing for native atrial depolarization), or synchronously add paced atrial and ventricular beats (in the setting of SND or asystole)

- VOO or DOO: are commonly employed "asynchronous" pacing modes in which the device paces without respect to native conduction. These modes are usually only employed for limited periods (e.g., surgeries, emergencies) in which there is high possibility for errors in sensing

■ **Special terminology**:

- Rate-modulation: also referred to as 'rate responsiveness' or 'rate adaptation,' rate modulation is a programmable device feature in which the pacing rate varies dependent upon patient activity, as detected by device sensors
- Hysteresis: also called AV-search hysteresis, this is a feature available in dual-chamber devices in the DDD mode in which the pacemaker will periodically lower its pacing rates in order to allow for potential intrinsic activity below the programmed lower rate (or sensor rate). It is often misinterpreted for oversensing with pauses.

Additional Indications

■ The most common indications for pacemaker device therapy is SND or AV block.
■ There has also been active research regarding specific indications for pacing beyond conventional SND or AV block. Some of these are briefly outlined below (see Table 16-4)

TABLE 16-4

ACC/AHA/HRS RECOMMENDATIONS FOR PERMANENT PACING IN SPECIFIC CONDITIONS

Recommendations for pacing in hypersensitive carotid sinus syndrome and neurocardiogenic syncope
Recurrent syncope caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole of ≥3 s (Class I)
Reasonable for syncope without clear, provocative events and with a hypersensitive *cardioinhibitory* response of ≥3 s (Class IIa)
May be considered for significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing (Class IIb)
Recommendations for pacing after cardiac transplantation
Persistent inappropriate or symptomatic bradycardia not expected to resolve and for other Class I indications for permanent pacing (Class I)
May be considered when relative bradycardia is prolonged or recurrent, which limits rehabilitation or discharge after postoperative recovery from cardiac transplantation (Class IIb)
Recommendations for pacing in neuromuscular diseases
Permanent pacemaker implantation may be considered in the setting of neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with bifascicular block or any fascicular block, with and without symptoms (Class IIb)
Recommendations for pacing to prevent tachycardia
Sustained pause-dependent VT, with or without QT prolongation (Class I)
Reasonable in high-risk patients with the **congenital long-QT syndrome** (Class IIa)
May be considered for prevention of symptomatic, drug-refractory, recurrent AF in patients with coexisting SND (Class IIb)
Recommendations for pacing in patients with hypertro phic cardiomyopathy (HCM)
Indicated for SND or AV block in patients with HCM per usual indications (Class I)
May be considered in medically refractory symptomatic patients with HCM and significant resting or provoked LV outflow tract gradient. When risk factors for SCD are present, consider DDD-ICD placement (Class IIb)
Recommendations for permanent pacing in children, adolescents, and patients with congenital heart disease
Indicated for advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output (Class I)
Indicated for SND with correlation of symptoms during age-inappropriate bradycardia (Class I)
Indicated for postoperative advanced second- or third-degree AV block not expected to resolve or that persists at least 7 days after cardiac surgery (Class I)
Indicated for congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction (Class I)
Indicated for congenital third-degree AV block in the infant with a ventricular rate ≤55 bpm or with congenital heart disease and a ventricular rate ≤70 bpm (Class I)

SND sinus node dysfunction, *AV* atrioventricular, *SVT* supraventricular tachycardia, *VT* ventricular tachycardia, *MI* myocardial infarction

Adapted from the "2008 ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities." JACC 2008; 51: e1-e62 (4)

CARDIAC RESYNCHRONIZATION THERAPY (CRT)

Although pacemakers have been conventionally used in the primary treatment of arrhythmia, pacing for hemodynamic indication has been recognized of increasing importance in patients with heart failure due to systolic left ventricular (LV) dysfunction.

Background

- CRT is the use of a biventricular pacemaker with three electrical leads to coordinate myocardial contraction.

- Two leads are endocardial, placed in the right atrium (RA) and right ventricle (RV), while a third lead is placed in a tributary of the coronary sinus overlying the epicardial surface of the LV.
- CRT exerts its physiological impact via synchronizing ventricular contraction, leading to improved left ventricular filling, reverse remodeling with reduced left ventricular volumes and increased ejection fraction, and reducing functional mitral regurgitation.

Impact

Multiple prospective randomized studies have shown that CRT yields long-term clinical benefits, including improved quality of life, increased exercise capacity, reduced heart failure hospitalization and decreased all-cause mortality [23–28] in patients meeting traditional CRT criteria (New York Heart Association (NYHA) Class II–IV, LV ejection fraction (LVEF) ≤35%, QRS width ≥120 ms) [29, 30]. Note: *HF symptom status should be assessed after medical therapy has been optimized for at least 3 months.*

Patient-Selection

Beyond traditional criteria for CRT, there are subsets of patients who derive particularly substantial benefit

- Female patients
- LBBB morphology
- QRS width ≥150 ms
- Patients with history of non-ischemic cardiomyopathy

Recommendations

ACC/AHA/Heart Rhythm Society (HRS) Recommendations

- Class I
  - In patients with NYHA Class II, III or ambulatory Class IV heart failure symptoms, LVEF ≤35%, LBBB, QRS ≥150 ms, and sinus rhythm, CRT with or without implantable cardioverter defibrillator (ICD) is indicated
  - Class II
    - CRT reasonable in similar patients to above with LBBB and QRS 120–149 ms (IIa) or non-LBBB and QRS ≥150 ms (IIa)
    - CRT reasonable in similar patients as above in AF if (a) patient requires ventricular pacing and (b) AV node ablation or pharmacologic rate control will allow near 100% biventricular pacing (Class IIa)
    - CRT can be useful in patients with LVEF ≤35% undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing.
    - CRT may be considered for patients with NYHA Class I symptoms, ischemic etiology of heart failure, LVEF ≤30%, sinus rhythm, LBBB and QRS ≥150 ms (class IIb)
    - CRT may be considered for patients with LVEF ≤35%, sinus rhythm, non-LBBB, NYHA class III/ambulatory class IV, and QRS 120–149 ms (IIb) or similar non-LBBB with NYHA II symptoms and QRS ≥150 ms (IIb)
  - Class III
    - CRT not indicated for asymptomatic patients with reduced LVEF in absence of other indications for pacing
    - CRT not indicated for patients whose functional status and life expectancy are limited by predominantly noncardiac conditions

Biventricular Pacing in Patients with atrioventricular block and Systolic Dysfunction
Based on randomized controlled data (BLOCK-HF), biventricular pacing was superior to conventional right ventricular pacing in patients with atrioventricular block and LV systolic dysfunction (LVEF < 50%) with NYHA I–III HF symptoms [31]. The primary benefit was a reduction in HF related hospitalizations.

QUICK REVIEW

TOPIC	KEY POINTS
Etiology of bradyarrhythmia	Can be broadly classified into (a) failure of impulse generation or (b) impulse propagation
Primary cause of bradyarrhythmias due to failure of impulse generation	Sinus node dysfunction
SND is characterized by:	1. Frequent sinus pauses, sinus arrest, or sinus exit block 2. Inappropriate sinus bradycardia with chronotropic incompetence 3. Episodes of bradycardia alternating with atrial tachyarrhythmias 4. AF with slow ventricular response or very slow recovery after conversion
Treatment of choice for SND:	PPM
Selected indications:	*Symptomatic* bradycardia *Symptomatic* chronotropic incompetence
Primary cause of bradyarrhythmias due to failure of impulse propagation	Atrioventricular block
Types of AV block:	1. First-degree AV block (usually supranodal) 2. Second-degree AV block a. Mobitz I/Wenkebach (usually at the level of the node) b. Mobitz II (often infranodal) 3. Third-degree AV block (usually infranodal)
Treatment of choice for AV block:	*'Advanced-AV block' or 'advanced second-degree AV block' refers to second-degree AV block with multiple nonconducted beats*
Selected indications:	Eliminate offending agent; consider PPM Advanced second- or third-degree AV block with *symptomatic* bradycardia, ≥3 s pauses in NSR, ≥5 s pauses in AF, or escape rate <40 bpm
Selected specific situations beyond SND or AV block that require pacing	■ *Carotid sinus hypersensitivity*: recurrent syncope, documented ≥3 s aystolic pauses with regular activity, and predominant cardioinhibitory response ■ *After anterior MI:* alternating bundle-branch block ■ *After cardiac transplantation:* persistent inappropriate sinus bradycardia ■ *To prevent tachycardia:* due to pause-dependent with or without QT prolongation and in high-risk patients with congenital long QT syndrome ■ *In hypertrophic cardiomyopathy (HCM):* may be considered in medically refractory symptomatic patients with HCM and significant resting or provoked LV outflow gradient
Indications for CRT	■ LVEF ≤35% ■ NYHA Class II, III, ambulatory class IV on optimal medical therapy ■ QRS ≥150 ms, LBBB (Class I) ■ QRS 120–149 ms, LBBB or QRS ≥150 ms, non-LBBB (Class IIa) ■ LVEF ≤35% with anticipated RV pacing >40% or LVEF <50%, NYHA I–III and complete AV block (BLOCK-HF)

QUESTIONS AND ANSWERS

Question 1

A 21-year-old male was found down outside of a college dormitory. An automated external defibrillator placed in the field recommended defibrillation. He converted to sinus bradycardia at 35 beats per minute after one shock. He was subsequently transported to the hospital where therapeutic hypothermia was initiated. On physical exam he was intubated and nonresponsive to painful stimuli. His pupils were dilated, but reactive to light symmetrically. His past medical history is notable for two prior fainting episode in adolescence after diving into a cold pool. His parents deny knowledge of a history of substance abuse. His family history is notable for a brother who died suddenly at the age of 32. On echocardiography, he was found to demonstrate a reduced left ventricular ejection fraction of 25% with normal wall thickness and without evidence of asymmetric left ventricular hypertrophy. No significant valvular abnormalities were noted. ECG on presentation was notable for a QT of 600 ms (QTc 458 ms) and intraventricular conduction delay with QRS width of 130 ms. The patient's resting HR remained in normal sinus, but remained below 45 beats per minute even after return of normothermia and complete neurological recovery.

All of the following statements are true except?

A. The patient meets secondary-prevention criteria for an implantable cardioverter-defibrillator due to aborted sudden cardiac death.
B. The patient meets criteria for cardiac resynchronization therapy given his low ejection fraction and QRS width >120 ms.
C. The patient's family history of sudden cardiac death is a pertinent risk factor.
D. The patient will require a dual-chamber chamber pacemaker.
E. Medical therapy with beta-blockade should be initiated.

Answer

1. The correct answer is A

This patient demonstrates classic findings of the congenital long QT syndrome. The description of a prior syncopal episode while swimming is characteristic of an Long QT syndrome type 1 (LQT1)-type trigger. LQT1 is the most common form of congenital long QT syndrome, and is due to a loss-of-function mutation in KCNQ1, which encodes IKs. The patient's current presentation is consistent with an aborted sudden-cardiac death event. Polymorphic Ventricular tachycardia (VT) (i.e., torsades de pointes) was the likely inciting ventricular arrhythmia. The mainstays of therapy include beta-blockade, which suppresses the adrenergic surge which leads to polymorphic VT. In addition, there is a role for DDD pacing in some patients who exhibit pause-dependent VT. Although this cannot yet be substantiated in this patient, he demonstrates an inappropriate degree of bradycardia, which would likely worsen after beta-blockade. If his LVEF does not recover after this event over time, he may eventually become a candidate for CRT, although his heart failure symptom status cannot be established from this event (at least 3 months must progress on optimal medical therapy, including titrating of diuretic therapy to maintain normal volume status).

Question 2

An 84-year-old woman presents to her primary care physician with complaints of near-fainting spells and "lack of pep." Her past medical history is only notable for hypertension, for which she is maintained on propranolol extended release once daily. She is found to demonstrate normal sinus rhythm on her ECG with a heart rate of 65 beats per minute. She reports feeling reasonably well at home while in bed watching TV, but is often light-headed with quick standing or while reaching/bending over to clean. A tilt-table test is performed which reveals cardioinhibitory response and bradycardia. The patient is awake throughout testing, and reports feeling fatigued, but is conversant throughout. When asked to walk on a treadmill, the patient's HR increases to 70 beats per minute and she again asks to stop due to fatigue.

Which of the following statements are true?

A. The patient meets criteria for a permanent pacemaker to treat the hypersensitive carotid sinus syndrome.
B. The patient meets criteria for a permanent pacemaker due to symptomatic bradycardia.
C. The patient meets criteria for a permanent pacemaker due to symptomatic chronotropic incompetence.
D. The patient will require a dual-chamber chamber pacemaker.
E. Definitive recommendation regarding permanent pacing cannot be made at this point.

Answer

1. The correct answer is E

The patient demonstrates features suggestive of the carotid sinus syndrome (symptoms while stretching/bending) and with a concerning tilt-table test result. With that said, she reports no history of frank syncope and demonstrated only lightheadedness when bradycardic during testing. A history of syncope is mandated in order to meet Class I or II indication for permanent pacing. The patient does demonstrate evidence of chronotropic incompetence on treadmill testing and this is likely the primary cause of her symptoms. With that said, however, her beta-blocker has not yet been discontinued and recommendation regarding pacing cannot be made until all potentially offending agents have been discontinued. In this woman's case, her past medical history does not mandate therapy with nodal blocking agents, and an alternative antihypertensive could be employed.

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CHAPTER 17

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Ventricular Arrhythmias, Defibrillators, Sudden Cardiac Death and Syncope

CONTENTS

ABBREVIATIONS

AAD	Anti-arrhythmic drugs
ACC	American College of Cardiology
ACE-I	Angiotensin converting enzyme inhibitor
AHA	American Heart Association
ARVC	Arrhythmogenic right ventricular cardiomyopathy
AS	Aortic stenosis
AV	Atrioventricular
BB	Beta blocker
BP	Blood pressure
bpm	Beats per minute
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCB	Calcium channel blocker
CEA	Carotid endarterectomy
CHF	Congestive Heart Failure
CSM	Carotid Sinus Massage
CT	Computed Tomography
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection Fraction
EPS	Electrophysiology study
GDMT	Goal directed medical therapy
HOCM	Hypertrophic obstructive cardiomyopathy
HR	Heart rate
HRS	Heart Rhythm Society
ICD	Implantable cardioverter defibrillator
LOC	Loss of consciousness
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging

MS	Mitral stenosis
NMS	Neurally mediated syncope
NSVT	Non-sustained ventricular tachycardia
NYHA	New York Heart Association
PCM	Physical counter-pressure maneuvers
PE	Pulmonary embolus
POTS	Postural orthostatic tachycardia syndrome
PS	Pulmonic stenosis
PVR	Peripheral vascular resistance
RV	Right ventricle
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SHD	Structural heart disease
SSS	Sick sinus syndrome
SVT	Supraventricular tachyarrhythmia
TIA	Transient Ischemic Attack
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White

DISTINGUISHING WIDE QRS COMPLEX TACHYCARDIAS

History: A prior history of structural or coronary heart disease favors ventricular tachycardia (VT).

Clinical exam: Neither hemodynamic stability nor physical exam findings are of sufficient specificity to be relied upon in order to distinguish between wide QRS complex tachycardia etiologies.

- Jugular venous exam may reveal cannon "a" waves due to atrioventricular dissociation in patients with VT.
- Variable intensity of the first heart sound favors VT due to variation in the A-V relationship.
- A third heart sound may favor VT but is not specific enough to diagnose VT.

Differential diagnosis:

- Ventricular tachycardia
- Supraventricular tachycardia with aberrancy
- Pre-excitation
- Other causes: adverse medication reactions (e.g., digitalis toxicity [specifically associated with bidirectional VT], class IC agents), ventricular pacing with atrial arrhythmia, metabolic derangement (e.g., hyperkalemia)

The 12-lead ECG is the most useful to identify VT from SVT with aberrancy and should be obtained if the patient is hemodynamically stable.

Discrimination of VT from SVT with aberrancy:

- Helpful factors are detailed in Table 17-1
- Atrioventricular dissociation is the sine qua non of VT, often manifest as capture or fusion beats on the ECG. However the absence of evident atrioventricular dissociation does not exclude VT (i.e. atrial fibrillation).
- Additional factors favoring VT [2, 3]:

TABLE 17-1

STEPWISE ALGORITHM FOR DISCRIMINATING VT FROM SVT WITH ABERRANT CONDUCTION [1]

	SENSITIVITY FOR VT	SPECIFICITY FOR VT
1. Absence of RS complex in all precordial leads (negative precordial concordance)	0.21	1.0
2. R to S interval >100 ms in any precordial lead	0.66	0.98
3. AV dissociation	0.82	0.98
4. Morphology criteria for VT in V1-2 and V6[a]	0.99	0.97
OVERALL ALGORITHM	0.97	0.99

[a]If RBBB pattern in V1, VT favored if: V1 has monophasic R, qR, or R > R′ in RSR′ pattern, RS in V6
If LBBB pattern in V1, VT favored if: R in V1 > 40 ms, notched S in V1 or V2, onset to nadir > 60 ms in V1, Q or QS in V6

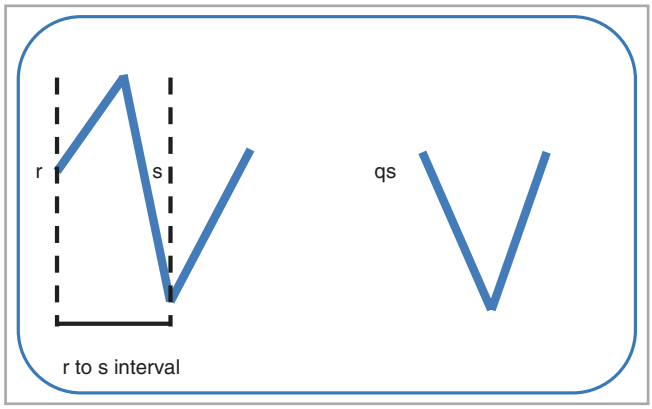

FIGURE 17-1

The rs interval is defined as the duration spanning the onset of the r wave and the trough of the s wave. A qs wave is depicted without any demonstrable r wave

- QRS duration >160 ms
- Right superior QRS axis (−90° to ±180°)
- Concordance in the precordial leads

Table 17-1
Figure 17-1

CLASSIFICATION OF VENTRICULAR ARRHYTHMIAS

Table 17-2
Figure 17-2
Figure 17-3
Figure 17-4
Figure 17-5

TABLE 17-2

CLASSIFICATION OF VENTRICULAR ARRHYTHMIAS

ARRHYTHMIA	ASSOCIATED FEATURES
Post-infarction ventricular tachycardia (Fig. 17-2)	■ Mechanism often reentry around scar ■ Typically monomorphic unless associated with active ischemia ■ Associated wall motion abnormalities and left ventricular dysfunction on imaging ■ Management: GDMT, revascularization if possible, ICD if candidate, antiarrhythmics, catheter ablation
Idiopathic ventricular tachycardia	
Outflow tract tachycardias (Fig. 17-3)	■ Cyclic adenosine monophosphate mediated delayed afterdepolarizations, triggered activity ■ Inferior axis, often left bundle branch block morphology during tachycardia ■ More common in women, can be exacerbated with exercise and in pregnancy ■ Adenosine, calcium channel blocker, or beta-blocker sensitive ■ Treatable with meds or catheter ablation ■ Benign prognosis
Fascicular tachycardias (Fig. 17-4)	■ Reentry involving Purkinje tissue ■ Right bundle branch block, left anterior fascicular block or left posterior fascicular block pattern during tachycardia ■ More common in men ■ Verapamil sensitive ■ Treatable with verapamil or catheter ablation ■ Benign prognosis
Ventricular tachycardia and congenital heart disease	■ Reentry often involving surgical patch, suture lines, or scar ■ May be amenable to ablation but ICDs often favored given structural disease
Other ventricular tachycardias	
Bundle branch reentrant ventricular tachycardia	■ Reentry involving the bundle branch fascicles ■ Typical left or right bundle branch block pattern ■ Associated with structural heart disease (e.g., dilated cardiomyopathy) ■ Poor response to pharmacologic therapy; catheter ablation is first-line therapy; ICDs appropriate as typically unstable
Arrhythmogenic right ventricular cardiomyopathy	■ Reentry around areas of fibrofatty tissue ■ LBBB pattern ■ Baseline ECG – May be essentially normal in some – 1st degree atrioventricular block – Epsilon wave (early afterdepolarization) – T wave inversion $V_{1\text{-}3}$ – Right bundle branch block or incomplete right bundle branch block, or prolonged S wave upstroke (>55 ms) in $V_{1\text{-}3}$ in absence of right bundle branch block ■ More common in young men, progressive disorder ■ Associated with desmosomal mutations; genetic testing may be useful ■ Typically exercise induced ventricular arrhythmias ■ Sotalol useful, avoidance of competitive sports, ICD in high-risk patients
Ventricular tachycardia in nonischemic cardiomyopathy	■ Reentry around deep myocardial scar or fibrosis
Polymorphic ventricular tachycardia and fibrillation (Fig. 17-5)	■ Reentry, automaticity, or triggered activity ■ Torsades de Pointes represents "twisting of the points" in context of a long QTc interval

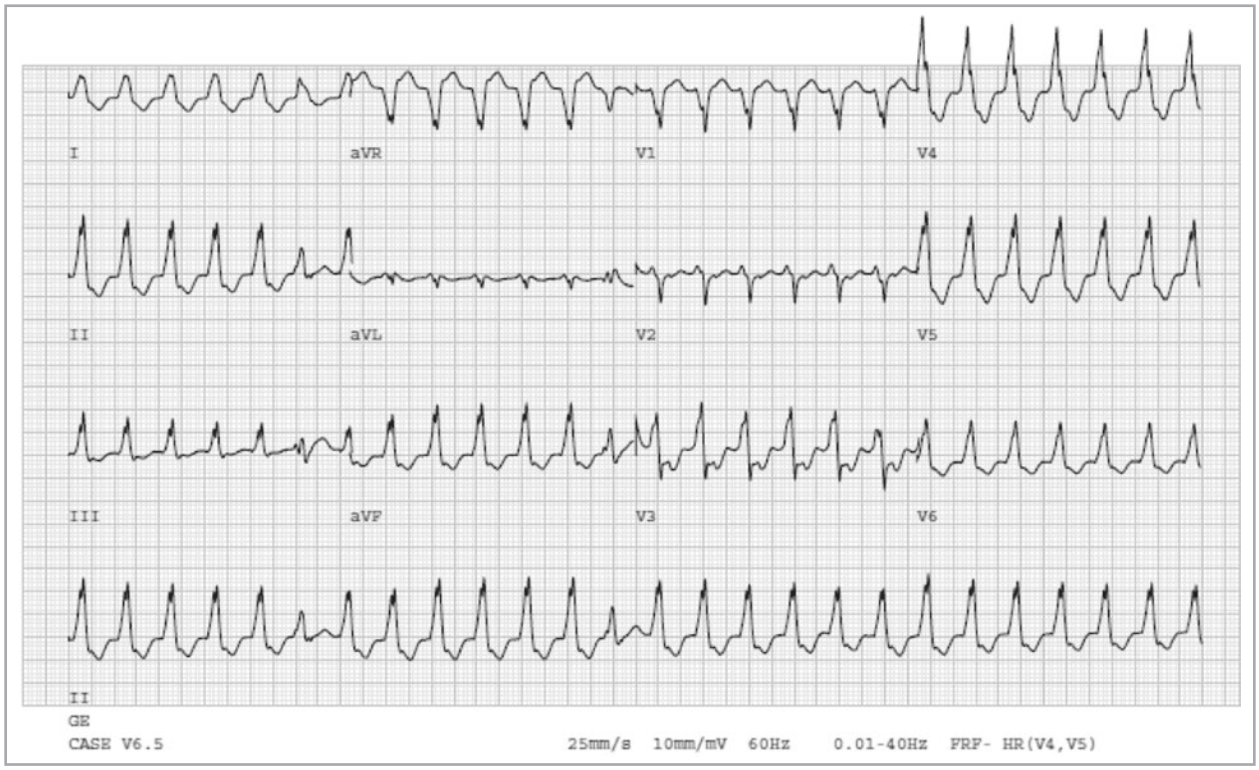

FIGURE 17-2

Exercise induced post-infraction scar-related monomorphic ventricular tachycardia in a patient with basal scar (note the fusion beats)

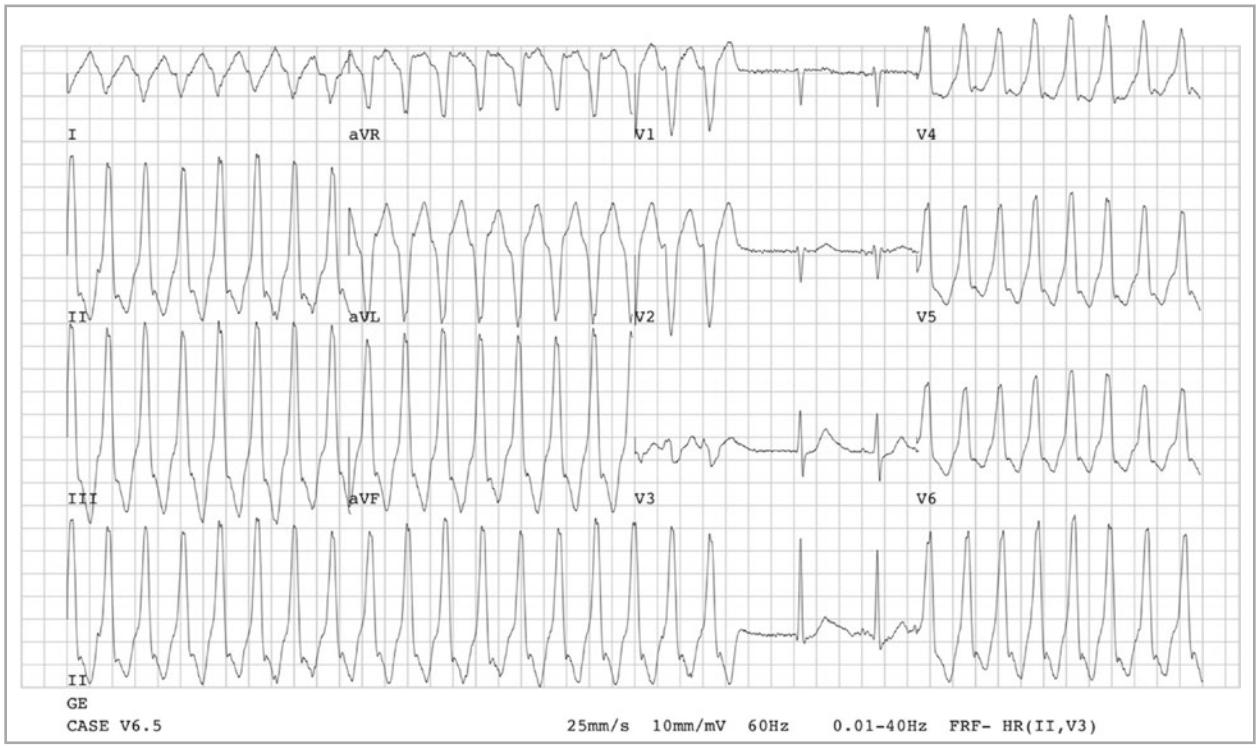

FIGURE 17-3

Exercise induced right ventricular outflow tract tachycardia manifesting with an inferior axis and left bundle branch block pattern. The tachycardia terminates and then resumes

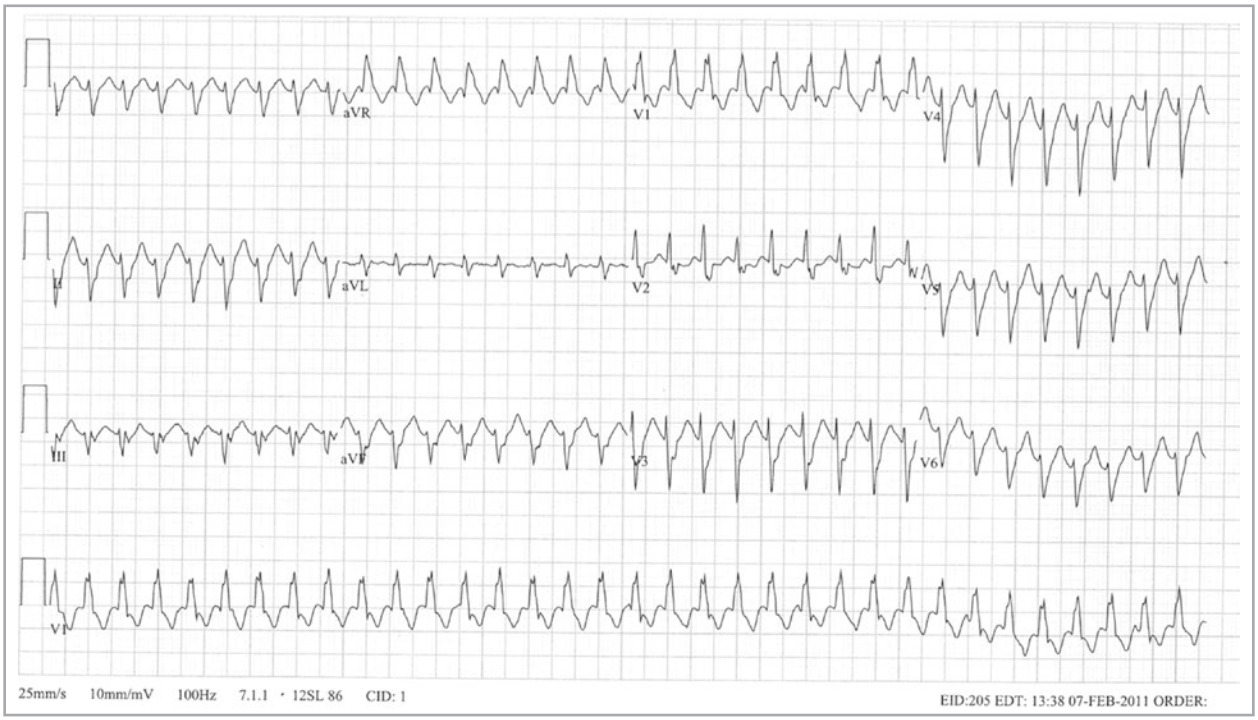

FIGURE 17-4

Fascicular ventricular tachycardia with a right bundle branch block and right superior axis pattern

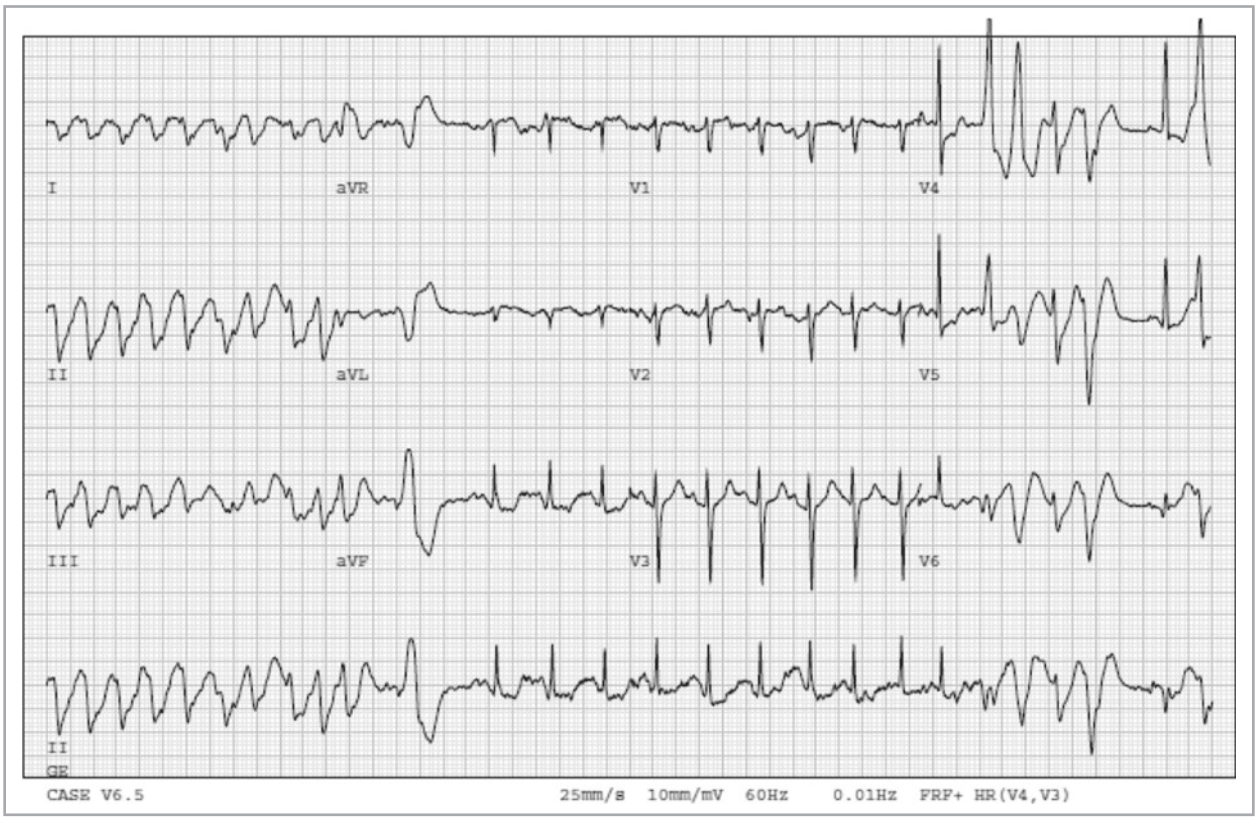

FIGURE 17-5

Exercise induced polymorphic ventricular tachycardia in a patient with left main coronary artery stenosis and myocardial ischemia

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Trials

Table 17-3

TABLE 17-3

MAJOR ICD TRIALS

STUDY	YEAR	LEFT VENTRICULAR EJECTION FRACTION (LVEF) (%)	KEY TRIAL/INCLUSION CHARACTERISTICS	RELATIVE RISK FOR ICD (95% CONFIDENCE INTERVAL)
Primary prevention				
MADIT I [4]	1996	≤35	*ICD vs. conventional care* ■ Prior myocardial infarction (MI) ■ Nonsustained ventricular tachycardia (NSVT) ■ Electrophysiology study (EPS) inducible VT/ventricular fibrillation (VF) not suppressible with antiarrhythmic drugs (AADs)	0.46 (0.26–0.82)
CABG-Patch [5]	1997	<36	*ICD vs. conventional care at time of coronary artery bypass grafting (CABG)* ■ Scheduled CABG ■ Abnormal signal averaged electrocardiogram	1.07 (0.87–1.42)
MUSTT [6]	1999	≤40	*EPS guided antiarrhythmic (AAD ± ICD) therapy vs. nonantiarrhythmic therapy* ■ Coronary artery disease ■ NSVT (≥4 days from most recent revascularization procedure) ■ EPS-inducible VT/VF	0.80 (0.60–1.01) EPS vs. nonantiarrhythmic 0.45 (0.32–0.63) ICD vs. nonantiarrhythmic
MADIT II [7]	2002	≤30	*ICD vs. conventional care* ■ Prior MI > (1 month prior) ■ No coronary revascularization ≤3 months prior	0.69 (0.51–0.93)
DEFINITE [8]	2004	<36	*ICD vs. conventional care* ■ Nonischemic cardiomyopathy ■ NSVT, VT, or moderate number of premature ventricular contractions	0.65 (0.40–1.06)
DINAMIT [9]	2004	≤35	*ICD vs. conventional care* ■ Recent MI (6–40 days) ■ Impaired heart rate variability	1.08 (0.76–1.55)
SCD-HeFT [10]	2005	≤35	*ICD vs. amiodarone vs. placebo* ■ Prior MI or nonischemic ■ NYHA II or III	0.77 (0.62–0.96) ICD vs. placebo
IRIS [11]	2009	Mean ~35	*ICD vs. conventional care* ■ Recent MI (<31 days) ■ LVEF ≤40 and heart rate >90, or NSVT	1.04 (0.81–1.35)
DANISH [12]	2016	≤35	*ICD vs. conventional care* ■ Non-ischemic ■ NYHA II, III, or IV (if CRT indicated)	0.87 (0.68–1.12)
Secondary prevention for sudden cardiac death				
AVID [13]	1997	≤40	*ICD vs. antiarrhythmic (sotalol or amiodarone)* ■ Prior cardiac arrest	0.62 (0.43–0.82)
CASH [14]	2000	Mean ~ 45	*ICD vs. antiarrhythmic (propafenone or metoprolol or amiodarone)* ■ Prior cardiac arrest	0.77 (1.11, upper bounds of 97.5%CI)
CIDS [15]	2000	Mean ~ 34	*ICD vs. amiodarone* ■ Prior cardiac arrest, syncope due to presumed VT	0.82 (0.60–1.10)

B) **Consensus guideline recommendations**

Table 17-4
Table 17-5

SYNCOPE

Definition

- Sudden, non-traumatic transient loss of consciousness (LOC) associated with a loss of postural tone followed by spontaneous complete recovery. If CPR needed, manage as SCD

Approach

- History, physical examination and ECG
- Differentiation of true syncope from other entities: seizure, SCD, TIA, etc.
- Risk stratification—any high risk features that may warrant admission/workup?
- Determination of etiology with or without additional studies

Etiologies (Table 17-6)

- **Neurally-mediated syncope**—Most common cause (~21%) [17]
  - **Normal physiology:** venous pooling → ↓ in venous return to right ventricle (RV) → ↓ stretch activation of cardiac mechanoreceptors (C fibers) reflexively ↑ sympathetic stimulation → ↑ HR, diastolic blood pressure (DBP), stable to ↓ systolic blood pressure (SBP) [18]

TABLE 17-4

AMERICAN HEART ASSOCIATION/ AMERICAN COLLEGE OF CARDIOLOGY/HEART RHYTHM SOCIETY (AHA/ACC/HRS) GUIDELINE INDICATIONS FOR ICD IMPLANTATION [16]

Class I recommendations (Indicated)
■ Cardiac arrest due to VT/VF without a reversible cause
■ Structural heart disease and spontaneous sustained VT
■ Syncope of undetermined origin with inducible VT/VF at EPS
■ LVEF ≤ 35% due to prior MI ≥ 40 days ago with NYHA class II or III symptoms
■ LVEF ≤ 35% due to non-ischemic cardiomyopathy with NYHA class II or III symptoms
■ LVEF ≤ 30% due to prior MI ≥ 40 days ago with NYHA class I symptoms
■ LVEF ≤ 40% due to prior MI and nonsustained VT with inducible VT/VF at EPS
Class III recommendations (Contraindicated)
■ Expected survival < 1 year with poor functional status
■ Incessant VT/VF
■ Significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up
■ NYHA Class IV heart failure with drug-refractory symptoms who are not candidates for cardiac transplantation or cardiac resynchronization and defibrillator therapy
■ Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease
■ When VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with Wolff-Parkinson-White syndrome, right or left ventricular outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease
■ Ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma)

TABLE 17-5

COMMON ANTIARRHYTHMIC MEDICATIONS

DRUG (CLASS)	USES	ELECTROPHYSIOLOGIC EFFECTS	CONTRAINDICATIONS	COMMON ADVERSE EFFECTS
Procainamide (IA)	VT, pre-excited AF	↑ QRS, ↑ QTc		TdP, hypotension
Quinidine (IA)	VF, TdP, Brugada	↑ QRS, ↑ QTc	Cirrhosis	TdP, syncope, AV block,
Lidocaine, Mexiletine (IB)	VT, VF, PVC	↑ QRS at high levels		Hypotension, delirium, parasthesias
Flecainide, Propafenone (IC)	AF, PVC (without structural heart disease)	↑ QRS, ↑ PR, ↓ sinus rate	Structural heart disease; use without nodal blockade	Sinus node dysfunction, MMVT with structural heart disease
Beta-blockers (II)	SVT, AF, VT, PVC, LQTS	↓ sinus rate, ↑ AVN refractoriness	Cardiogenic shock	Hypotension, bradycardia, AV block
Amiodarone (III)	VT, VF, PVC, AF, SVT	↑ QRS, ↑ QTc, ↓ sinus rate, ↑ AVN refractoriness	Relative: pre-existing thyroid, liver, lung disease	TdP, hypotension, Thyroid, liver, lung toxicity
Dofetilide (III)	AF	↑ QTc	Renal dysfunction, prolonged QTc	TdP
Dronedarone (III)	AF	↑ QTc	CHF, high grade AV block, prolonged QTc	CHF, TdP
Sotalol (III)	VT, VF, PVC, AF	↑ QTc, ↓ sinus rate, ↑ AVN refractoriness	Renal dysfunction, prolonged QTc	TdP, hypotension, bradycardia
Diltiazem (IV)	SVT, AF, VT (RVOT)	↓ sinus rate, ↑ AVN refractoriness	Cardiogenic shock	Hypotension, bradycardia, AV block
Verapamil (IV)	SVT, AF, VT (RVOT), fasicular VT	↓ sinus rate, ↑ AVN refractoriness	Cardiogenic shock	Hypotension, bradycardia, AV block

– **Vasovagal syncope (AKA Neurocardiogenic)**

■ **Vasovagal pathophysiology:** ↓ in venous return → vigorous right ventricular contraction →large number of C fibers stimulated → ↑ neural output to brainstem → ↓ HR and PVR. Mechanoreceptors found in esophagus, lung, rectum, bladder [18]

– Cardioinhibitory: predominance of bradycardia or asystole
– Vasodepressor: hypotension resulting from insufficient sympathetic vasoconstriction

■ **History**:

– Position: usually upright
– Prodrome: fatigue, dizziness, weakness, nausea, diaphoresis, vision changes (tunnel vision), headache, abdominal discomfort, loss of hearing, "lack of air"
– LOC: usually <20 s
– Post-syncope: rapid return of alertness and orientation, fatigue or weakness may persist

TABLE 17-6

CAUSES OF SYNCOPE

ETIOLOGY OF SYNCOPE, *MEAN PREVALENCE (RANGE)*
Neurally mediated *(~20%)*
■ Vasovagal *14 (8–37)%*
■ Carotid Sinus Syncope *1%*
■ Situational *3 (1–8)%*
– Micturition
– Defecation
– Cough
– Swallowing
– Postprandial
– Post exercise
– Increased intrathoracic pressure: e.g. weightlifting, trumpet playing
■ Neuralgia
– Trigeminal
– Glossopharyngeal
Orthostatic hypotension *11 (4–13)%*
Drug-Induced or Associated Syncope *3 (0–7)%*
Cardiac
■ Mechanical *3 (1–8)%*
– Obstruction to LV flow
AS, HOCM, MS, LA myxoma
– Obstruction to pulmonary flow
PH, PE, Tetralogy of Fallot, PS, RA myxoma
– Pump failure due to MI or advanced cardiomyopathy
– Cardiac tamponade
– Aortic dissection
■ Electrical *14 (4–26)%*
– Bradyarrhythmias
Sick sinus syndrome
2nd or 3rd degree heart block, bifasicular block
Medication effect: beta-blocker, antiarrhythmic CCB
Pacemaker malfunction
– Tachyarrhythmias
Supraventricular tachycardia
Ventricular tachycardia/VF
Torsades de Pointes
Neurologic causes of transient loss of consciousness *7 (3–32)%*
■ Seizures
■ Transient ischemic attacks
■ Migraines
■ Subclavian steal
Psychiatric *1 (0–5)%*
Unknown *39 (13–42)%*

AS Aortic stenosis, *LA* left atrial, *LV* left ventricular, *MI* myocardial infarct, *MS* mitral stenosis, *PE* pulmonary embolism, *PH* pulmonary hypertension, *PS* pulmonic stenosis, *RA* right atrial

- Exam: pallor, diaphoresis, cold skin, dilated pupils, witnesses may describe motor activity (e.g. clonic jerking) **AFTER** LOC

– **Carotid Sinus Syncope (1%)**

- Inciting factors: external pressure on carotid (e.g. tight collar, shaving, sudden head turn)
- Typical patient: usually older, men > women
- Past medical History: History of head/neck tumor, scar tissue in neck
- Exam: Carotid sinus massage (CSM) (see physical exam)

– **Situational Syncope** (Table 17-6) [19]
– **Glossopharyngeal or Trigeminal Neuralgia**

■ **Orthostatic Syncope (~9%)**

– **Causes**

- **Hypovolemia**: dehydration, anemia, diarrhea
- **Medications**
- **Neurogenic orthostasis**
  - Diabetes, amyloidosis, tabes dorsalis, Sjögren's syndrome, Multiple-system atrophy with autonomic failure (Shy-Drager), paraneoplastic autonomic neuropathy, multiple sclerosis, Lewy body dementia, Parkinson's
  - Evaluation: consider autonomic testing

- **History**
  - Lightheadedness, weakness, nausea, visual changes, etc. in response to sudden postural change

■ **Cardiac Arrhythmia (~14%)**

– **Bradyarrhythmias**

- **Sinus node dysfunction**
  - Sick sinus syndrome (SSS) manifest as sinus bradycardia, pauses, sinoatrial exit block, chronotropic incompetence
- **Atrioventricular (AV) conduction disturbances**
  - AV nodal or distal conduction system disease
  - Includes Mobitz II, high grade AV block, or complete AV block
  - Rarely Mobitz I
  - Congenital AV block: block usually at level of AV node, with narrow QRS
- **Medication related:** antiarrhythmics, BB, CCB, digoxin
- **Pacemaker malfunction**
  - Causes: lead malfunction, battery depletion, R on T

– **Tachyarrhythmias**

- **Supraventricular Tachycardia (SVT)**
  - Factors that contribute to syncope: rate, volume status and posture of patient at onset, presence of associated heart disease, peripheral compensation
- **Ventricular Tachycardia (VT)/Ventricular Fibrillation (VF)**
  - Monomorphic VT: Most often due to ventricular scarring
    - Prior myocardial infarction
    - Sarcoidosis
    - Prior Myocarditis
    - Cardiomyopathies

- Hypertrophic cardiomyopathy
- Arrhythmogenic cardiomyopathy
- Dilated cardiomyopathy

- Polymorphic Tachycardia/Ventricular Fibrillation/
  - Etiologies
    - Ischemia
    - Torsades de Pointes: polymorphic arrhythmia with "twisting of the points" in the setting of long QT
      - Management: Mg, increase HR (temporary pacing, isoproterenol), avoid QT prolonging medications Channelopathies:
    - Channelopathies
      - Long QT syndrome
        - Diagnosis: QTc >500 ms on repeated ECGs in the absence of other explanations; QTc 480–500 in the presence of syncope; QT prolongation during exercise or epinephrine challenge
        - Treatment: avoid QT prolonging drugs, exercise restriction, beta-blockade, ICD if h/o cardiac arrest, recurrent syncope
      - Brugada syndrome
        - Diagnosis: Spontaneous Type I Brugada ECG, induced Type I with IV class I AAD
        - Treatment: ICD if h/o cardiac arrest, arrhythmic syncope, sustained VT. Asymptomatic Brugada ECG does not require ICD
    - Acquired QT prolongation (e.g., drugs [www.qtdrugs.org], hypokalemia, hypomagnesemia, etc.)

Structural Cardiac Disease (~4%)

- Valvular
  - Native Valve Obstructive lesions: Aortic Stenosis (AS), Mitral Stenosis (MS), Pulmonic Stenosis (PS), myxoma
  - Prosthetic Valve Issues: Thrombosis, Dehiscence, Malfunction
- **Myocardial**
  - LVOT obstruction: Hypertrophic Obstructive Cardiomyopathy (HOCM). Syncope ↑ risk of sudden cardiac death (SCD) (Relative Risk ~5), ICD recommended
  - Pump failure: Myocardial Infarction (MI) or congestive heart failure (CHF)
- **Pericardial:** Tamponade
- **Vascular**
  - Pulmonary Embolus (PE), Aortic dissection, Primary pulmonary hypertension
  - Coronary artery anomaly: anomalous course between aorta and pulmonary artery trunk highest risk

Neurologic Causes of Transient Loss of Consciousness (10%)

- **Seizure Disorders**
  - Transient LOC technically not syncope but often misdiagnosed
  - History: Table 17-6
  - Exam: Focal neurologic signs may suggest mass lesion
  - Evaluation:
    - Electroencephalogram (EEG)
    - Computed Tomography (CT)/Magnetic Resonance Imaging (MRI): Low utility in routine use, consider if witnessed seizure or focal neurologic sign

■ **Subclavian Steal** [15, 18]

- **Definition:** Subclavian artery stenosis proximal to origin of vertebral artery results in shunt of blood through cerebrovascular system → insufficient cerebral perfusion results when demands for circulation increases such as with arm exercise
- **History:** Syncope in setting of strenuous physical activity of one arm, history of Takayasu arteritis or cervical rib
- **Evaluation**: Color Doppler ultrasound, CT angiogram

Syncope Mimics (~2%)

■ **Causes**

- **Cataplexy**: Partial or complete loss of muscular control occurs triggered by emotions, especially laughter
- **Psychiatric**: **S**omatization disorders → conversion disorders, factitious disorder, malingering
- **Metabolic** : hypoglycemia, hypoxia, hypokalemia

Initial Evaluation (History, Physical Examination and ECG) (Fig. 17-6)

History (Patient and Witness If Available)

■ H&P identifies cause in ~45% of patients who are ultimately diagnosed

■ Initial findings suggestive of organic heart disease directed additional testing leading to diagnosis in ~8%

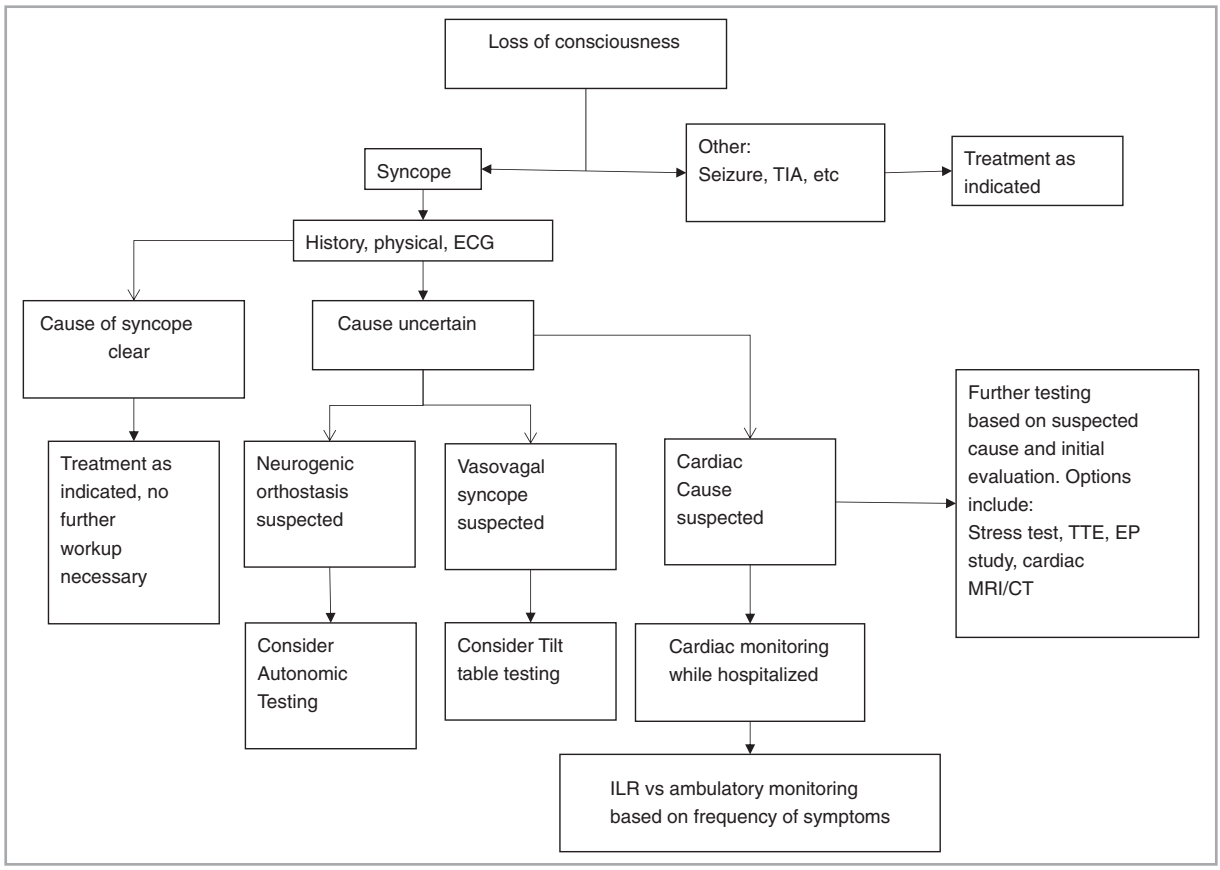

FIGURE 17-6

Proposed initial evaluation of syncope (adapted from [19])

- Helpful to differentiate between seizure and syncope (Table 17-7)
- **Basic Questions**
  - **Prior to event**: situational circumstances: position, activity prior to syncope, associated symptoms, prodrome
  - **During Event**: Activity during LOC, length of LOC, trauma
  - **Recovery After Event**: Assess for return of
- **Past Medical History**
  - **Prior syncope:** number, frequency and circumstances of previous episodes
    - Many and more frequent episodes suggest noncardiac cause
  - **Cardiac History**
    - History of SHD or arrhythmias, risk factors for CAD, PE
  - **Neurologic history**
    - History of and/or risk factors for seizures, stroke/TIA
  - **Other**
    - Metabolic disorders (i.e. diabetes, electrolyte abnormalities)
    - Recent bleeding history, trauma, dehydration
  - **Family History**
    - **Sudden Death**: early age is more worrisome
    - **Other cardiac diseases**: **c**ardiomyopathy, Relatives with pacemaker or ICD, congenital heart disease
  - **Social History**
    - **Drugs of abuse:** alcohol, opiates, marijuana
  - **Medications**
    - Antihypertensives (especially in elderly)
    - Central nervous system depressants (e.g. barbiturates)
    - QT prolonging agents (www.qtdrugs.org)
      - Type III antiarrhythmics, antipsychotics, antiemetics, methadone
      - Combinations may potentiate effects

TABLE 17-7

CLINICAL FEATURES THAT HELP DIFFERENTIATE CARDIAC VS. NON-CARDIAC CAUSES OF SYNCOPE AND SEIZURE

SUGGESTIVE OF CARDIAC CAUSE	SUGGESTIVE OF NON-CARDIAC CAUSE	SUGGESTIVE OF SEIZURE
Age > 60	Usually younger age	Waking with a cut tongue
Duration of warning ≤5 s	Prodrome or warning symptoms: n/v, warmth	Déjà vu or jamais vu prior to loss of consciousness
Male > Female	Female > Male	Associated with emotional stress
≤2 prior episodes of syncope	Similar prior episodes	Head turning during episode
Structural heart disease by history, exam, or echo	Situational triggers: cough, micturition, defecation	Unusual posturing or jerking limbs at start of and/or during episode
Exertional or supine syncope	Syncope with standing or position change	Prolonged confusion or amnesia after episode
Abnormal cardiac exam	No known cardiac disease	History of neurolgic disease

N/V Nausea, Vomiting

Physical Examination

Vital signs (INCLUDING Orthostatic Vital Signs)

- **Orthostatic vital signs**: Measure BP and HR after standing for 3 min or head-up tilt on tilt table
- Normal: SBP falls 5–15 mmHg, DBP rises slightly
- Orthostatic hypotension is present if:
  - SBP↓ 20 mmHg, DBP ↓ 10 mmHg, HR ↑ >10–20 bpm
  - Symptoms with standing
- **BP differential in arms: m**ay suggest subclavian stenosis, aortic dissection, or coarctation of aorta

Cardiac Exam

Neck Exam

- Carotid exam: pulse (may suggest AS), bruit
- Jugular venous pulsation
  - Elevation may suggest CHF
  - Cannon A waves may suggest arrhythmia

Auscultation

- S3 suggests CHF
- Pericardial rub may suggest pericardial effusion
- Murmurs including maneuvers to augment intensity (e.g. HOCM, AS)

Vascular Exam

- **Peripheral pulses**: Absent/diminished unilateral arm pulses may suggest subclavian steal

Neurologic Exam

- **Assess for focal neurologic deficits**
- **Carotid Sinus Massage**
- If history suggestive of carotid sinus hypersensitivity
- AVOID in patients with prior TIA or stroke within 3 months or if bruit present
  - Monitor patient with continuous ECG and BP measurement
- Protocol
  - In supine and upright positions, right carotid artery is firmly massaged for 5–10 s at anterior margin of sternocleidomastoid muscle at level of cricoid cartilage; if no 'positive' result, after 1–2 min repeat on left carotid artery
- Response
  - Cardioinhibitory—asystole of ≥3 s
  - Vasodepressor—↓ in SBP ≥50 mmHg

Electrocardiogram (ECG)

General Information

- Diagnostic of cause of syncope in ~5%
- Abnormal in 50% of syncope cases

Suggestive ECG findings of cardiac cause of syncope (Table 17-8)

TABLE 17-8

ECG FINDINGS SUGGESTIVE OF CARDIAC CAUSE OF SYNCOPE

ECG FINDINGS SUGGESTIVE OF CARDIAC CAUSE OF SYNCOPE
2nd (Mobitz II) or 3rd degree AV block
Marked sinus bradycardia (<40 beats/min) while awake
Sinus pause ≥3 s
Bifascicular block
IVCD (QRS > 120 ms without typical right or left bundle branch block morphology)
Abnormal QT interval
Preexcitation (i.e. WPW syndrome)
Brugada pattern (Right bundle branch block with ST elevation V1–V3)
T wave inversion V1–V3, epsilon waves and ventricular late potentials (i.e. ARVC)
Q waves suggesting prior MI or ST or T wave abnormalities suggesting ischemia/infarction
Evidence of pacemaker malfunction

AV Atrioventricular, *IVCD* Intraventricular Conductions Delay, *WPW* Wolff Parkinson White

Additional Diagnostic Evaluation

Echocardiogram

Diagnostic Utility

- Low diagnostic yield in absence of clinical, physical or ECG findings suggestive of cardiac abnormality
- Recommended if structural heart disease is suspected

Echo findings suggestive of possible syncopal etiology

- Valve disease—AS most common, MS, Prosthetic valve issues
- Cardiomyopathy—decreased ejection fraction (EF), HOCM, ARVC
- Wall motion abnormalities—suggestive of prior CAD
- Acute RV strain and/or pulmonary hypertension—suggestive of PE
- Cardiac Tumor—occasionally can obstruct blood flow
- Aortic Dissection—Transthoracic echocardiogram may miss ascending aortic dissection
- Congenital heart disease
  - In young, thin patients, can identify coronary ostia to assess for anomalous coronary arteries
- Cardiac Tamponade—atrial or RV inversion, respiratory variation in inflow velocities

Exercise Testing (ETT)

Diagnostic Utility

- Recommended for patients who experience syncope during or shortly after exertion
  - Use caution
  - *Exertional syncope patients should have echo prior to ETT to exclude HOCM*

Diagnostic ETT findings in syncope

- ECG and hemodynamic abnormalities present and syncope is reproduced during or immediately after exercise
- Mobitz II or 3rd degree AV block during exercise even in absence of syncope

- In patients <40 years old, drop in SBP with exercise, consider HOCM or left main coronary disease
- Screen for catecholaminergic polymorphic VT

Cardiac Rhythm Monitoring

Inpatient Cardiac Rhythm Monitoring: recommended for all patients with syncope of a suspected cardiac cause while hospitalized

Ambulatory Cardiac Rhythm Monitoring: see Table 17-9

Tilt Table Testing

Background

- Moving from supine to standing posture results in 15–20% decrease in plasma volume in 10 min, can induce vasovagal syncope in susceptible individuals with or without chemical stimulation
- Moderate sensitivity, specificity, and reproducibility
- **Positive response**—Syncope, asystole >3 s = cardioinhibitory

Indications (IIa)

- Suspected vasovagal syncope after initial evaluation is unclear
- Suspected delayed orthostatic hypotension when initial evaluation is unclear
- To distinguish convulsive syncope from epilepsy in selected patients
- To establish a diagnosis of pseudosyncope

TABLE 17-9

AMBULATORY CARDIAC RHYTHM MONITORING

MONITOR TYPE	FEATURES	PATIENT SELECTION
Holter	Continuous Monitoring 24–72 h Symptom Correlation	Frequent symptoms
Event Monitor	Patient activated recording Transmitted to central monitoring 2–6 week monitoring	Requires patient interaction (difficult with sudden onset syncope) Relatively frequent symptoms
External Loop Monitor	Continuous loop recording, patient and auto triggered Data transmitted to monitoring station 2–6 week monitoring	Syncope without significant prodrome Relatively frequent symptoms
External Patch Monitors	Continuous monitoring Symptom correlation No leads Record for 2–14 days	Data only available after patch removed Relatively frequent symptoms
Mobile Cardiac Outpatient Telemetry	Continuous monitoring Data transmitted to monitoring station	High risk patients where real time monitoring is preferred
Implantable Loop Recorder	Device implanted subcutaneously Patient or auto triggered Monitoring for up to 3 years Data transmitted to monitoring station or clinic	Recurrent, infrequent symptoms thought to be due to arrhythmias when initial workup negative

Contraindications (Class III)
- Treatment for vasovagal syncope
- To evaluate a high probability vasovagal event with no change in treatment if the study is positive

Electrophysiologic (EP) Study

Background
- Catheters assess sinus node function, AV conduction and susceptibility to SVT and VT

Indications (Class IIa)
- Evaluating syncope in patients with underlying cardiac disease or an abnormal ECG
- Positive results:
  - HV interval >100 ms
  - Inducible 2nd or 3rd degree AV block with atrial pacing
  - Inducible sustained VT >150 BPM
  - inducible sustained SVT>180 BPM

Contraindications (Class III)
- Patients with normal ECG and no heart disease or palpitations

Cardiac Imaging

- Limited utility—consider if concern for anomalous coronary anatomy

Neurologic Studies

- Autonomic testing can be helpful in selected patients with syncope that have known or suspected neurodegenerative disease
- Other routine neurologic testing (head CT, brain MRI, EEG, carotid ultrasounds) are of low diagnostic yield in patients with syncope (and not other forms of transient loss of consciousness)

Treatment

Individualized to Underlying Etiology of Syncope

Neurally mediated syncope
- Behavioral training
  - Education on warning signs and need to lay horizontal when symptoms to prevent injury
  - Techniques for avoiding syncope
    - Liberalize salt intake and maintain hydration
    - Avoidance of triggers for situational syncope
- Physical counter-pressure maneuvers (PCM)
  - Squatting, arm-tensing, leg-crossing and leg-crossing with lower body muscle tensing

Medications
- Few randomized clinical trials so insufficient evidence to support or refute use of ANY specific agents
- Potential classes
  - Volume expanders—e.g. fludrocortisone
    - Weak evidence (IIb) with potential side effects: hypertension, hypokalemia
  - Beta blocker: weak evidence (IIb)—theoretically lessen impact of adrenergic surge
  - Vaso/venoconstrictors
    - Midodrine has best evidence (IIa)
    - Side effects: hypertension, urinary retention

Device Therapy
- Dual chamber pacemakers have limited role in patients with predominantly cardioinhibitory (bradycardic) vasovagal syncope. They are less effective in patients with vasodepressor (hypotensive) vasovagal episodes
- Current recommendations (IIb): Patients >40 years of age with vasovagal syncope and documented symptomatic asystolic pauses >3 s during syncope or asymptomatic >6 s pauses

Orthostatic syncope
- Education about exacerbating factors for postural hypotension (i.e. sudden postural change, polypharmacy, diminished thirst in elderly, avoidance of triggers
- Hydration, volume expanders with close monitoring of blood pressure to avoid hypertension, PCM
- Vasoconstrictors
  - Midodrine has been shown to have effect in orthostatic syncope—caution with nocturnal/supine hypertension

Carotid sinus syncope [26]
- Avoidance of tight collars, neckties, abrupt neck movements
- **Device Therapy**: Cardiac pacing is reasonable (IIa) in patients with cardioinhibitory response to carotid sensitivity

Arrhythmias
- **Device Therapy**
- **Indications for pacing**
  - Benefit to pacemakers with symptomatic bradycardia or high risk for progression to heart block
  - ICD recommended in inducible sustained monomorphic VT in pt with syncope
  - ICD indications based on indications for arrhythmia and/or SHD, i.e. EF <35% (Table 17-4)

Prolonged QT
- Replete electrolytes (especially magnesium)
- Avoid QT prolonging drugs
- Beta blockade in long QT syndrome

TABLE 17-10

FACTORS AFFECTING TRIAGE OF PATIENTS PRESENTING WITH SYNCOPE

ADMISSION RECOMMENDED	ADMISSION OFTEN RECOMMENDED	POTENTIAL OUTPATIENT EVALUATION
History of and/or signs/symptoms suggesting MI, CHF, PE, aortic dissection or other SHD	Older than 65 years of age	Absence of structural heart disease and normal ECG
Exertional syncope, no prodrome, supine syncope, palpitations preceding syncope, or syncope causing trauma	History of SHD but no active evidence of disease	History of recurrent syncope over many years
Concerning ECG abnormalities (see Table 17-3)	Frequent spells	Suspicion of syncope "mimic" (e.g. hypoglycemia, conversion disorder)
Family history of early sudden cardiac death	Discontinuation or dose modification of offending drug	Suspected reflex syncope
History of and/or signs/symptoms of stroke or focal neurologic disorder	Moderate to severe orthostatic hypotension	
Suspected malfunction of cardiac device (pacemaker, ICD, prosthetic valve)		

CHF Congestive Heart Failure, *ICD* Implantable Cardioverter Defibrillator, *MI* Myocardial Infarction, *PE* Pulmonary Embolism, *SHD* Structural Heart Disease

Risk Stratification: Need for Hospitalization (Table 17-10)

QUICK REVIEW (TABLE 17-11)

TABLE 17-11

QUICK REVIEW

FINDING ON HISTORY OR EXAM	SUGGESTED DIAGNOSES
Occurred with prolonged standing	Vasovagal syncope
Associated with pain, fear, unpleasant sight, smell or sound	Vasovagal syncope
Occur in warm or crowded environment	Vasovagal syncope
Occurs with micturition, defecation, cough or deglutition	Situational/NMS
Occurs within an hour after eating	Postprandial hypotension
Occurs with head rotation, shaving, tight collars	Carotid hypersensitivity
Tonic-clonic movements short (<15 s) and occur AFTER loss of consciousness	Vasovagal syncope
Tonic-clonic movements prolonged and initiates DURING or PRIOR TO loss of consciousness	Seizure
Syncope associated with tongue biting, aching muscles, déjà vu, olfactory sensations and prolonged confusion	Seizure
Associated with throat or facial pain (glossopharyngeal or trigeminal neuralgia)	Neurally mediated syncope
Occurs with change of position from sitting to standing	Orthostatic hypotension
Taking one or more anti-hypertensive medications (especially polypharmacy in elderly)	Drug-induced syncope
Multiple medications prolonging QT or causing bradycardia	Drug-induced syncope
Well trained athlete with structurally NORMAL heart after exertion	Vasovagal syncope
Associated with vertigo, dysarthria, diplopia	TIA, stroke, vertebro-basilar insufficiency
Blood pressure difference between arms	Subclavian steal or aortic dissection
Syncope during arm exercise (e.g. painting a fence)	Subclavian steal
Occurs with change in position (upright to supine, bending over) ± murmur that also varies with position	Atrial myxoma, thrombus
Exertional syncope	Aortic stenosis, HOCM, mitral stenosis, pulmonary hypertension, CAD, or anomalous coronary artery
Supine syncope	Arrhythmia
Family history of sudden cardiac death	Long QT, Brugada, HOCM
Deaf patient with syncope after effort or strong emotion	Long QT syndrome
Triggered by laughter or strong emotions with normal cardiac evaluation	Cataplexy
Child <5 years old after frustrating episode or injury	Breath holding spell
Diabetic who skipped meals	Hypoglycemia

CAD coronary artery disease, *HOCM* hypertrophic obstructive cardiomyopathy

Questions and Answers

Question 1

A 64 year-old man presents with an acute anterior wall myocardial infarction. He undergoes urgent revascularization and a drug-eluting stent is placed to the proximal left anterior descending artery with an excellent angiographic result. There is sustained ventricular tachycardia degenerating into ventricular fibrillation during the catheterization requiring urgent defibrillation. He remains in the coronary care unit and receives diuresis for pulmonary edema. His electrocardiogram is notable for a left bundle branch block with a QRS of 180 ms. An echocardiogram the following day demonstrates a left ventricular ejection fraction of 20% with anterior wall hypokinesis; a previous echocardiogram demonstrated a normal ejection fraction. He improves clinically and is started on a beta-blocker, angiotensin converting enzyme inhibitor, and spironolactone. Which is the most accurate statement?

A. Implantation of a biventricular pacemaker and defibrillator is indicated at this time.
B. Implantation of a defibrillator is indicated because of the myocardial infarction and left ventricular ejection fraction below 30%.
C. Implantation of a defibrillator is indicated because of the myocardial infarction, left ventricular ejection fraction below 40%, and the episode of ventricular tachycardia.
D. Implantation of a defibrillator is not indicated at this time.

Answer
The correct answer is D.

Question 2

A 31 year-old woman and has been experiencing palpitations for the past two weeks. She denies any lightheadedness or syncope. An electrocardiogram reveals a wide complex tachycardia with a left bundle branch block morphology and inferior axis. Her workup including a 12-lead electrocardiogram performed in sinus rhythm, an echocardiogram, signal averaged electrocardiogram, and cardiac magnetic resonance imaging are normal. There is no family history of sudden cardiac death. Which of the following is the most appropriate next step?

A. Implantation of an internal cardioverter defibrillator.
B. Initiation of sotalol.
C. Addition of a beta blocker or calcium channel blocker and consideration of catheter ablation.
D. Initiation of amiodarone.

Answer
The correct answer is C.

Question 3

A 62 year-old man with a history of an anterior wall myocardial infarction 4 years prior has a left ventricular ejection fraction of 33% by echocardiogram. He has no angina and his prior percutaneous intervention site is patent without obstructive disease in the remaining coronary vessels. He is on maximum tolerable doses of a beta-blocker, angiotensin converting enzyme inhibitor, and spironolactone. He describes mild fatigue and dyspnea with moderate exertion. His electrocardiogram demonstrates sinus rhythm with a QRS of 90 ms, and a 5-beat run of nonsustained ventricular tachycardia. Which of the following is a correct statement?

A. An implantable cardioverter defibrillator is indicated because of the history of heart failure symptoms (NYHA class II–III), prior myocardial infarction, and a left ventricular ejection fraction ≤35%.
B. An implantable cardioverter defibrillator is indicated because of the history of nonsustained ventricular tachycardia and ischemic cardiomyopathy with a left ventricular ejection fraction ≤40%.
C. Antiarrhythmic therapy with amiodarone would be a reasonable alternative to implantable cardioverter defibrillator.
D. Implantation of a biventricular pacemaker and defibrillator is indicated at this time.

Answer
The correct answer is A.

Question 4

A 26 year-old female medical student passes out while standing up in an operating room. She states that prior to falling she felt weak, "warm all over" and sweaty. She also felt a "lack of air" but attributed it to her surgical mask. Witnesses stated she looked pale and gradually slumped to the floor. After falling the nurse noted a few jerking movements and she regained consciousness in about 5 s. The patient has no recollection for the event but states that she felt at her baseline almost immediately after awakening. She remembers passing out as a teenager, once on a hot summer day and after giving blood. She denies any medical problems, takes no medications and denies illicit drug use. Her grandfather had a heart attack at age 75 but otherwise denies family history of early coronary disease or sudden cardiac death. On physical examination, her HR is 65, BP 110/70, there is no jugular venous distention, normal pulse exam and cardiac exam. Her ECG reveals no abnormalities.

Which of the following is the next appropriate step?

A. Echocardiogram
B. Admission to hospital for further evaluation, including telemetry and cardiac biomarkers
C. Initiate beta blockade
D. Educate her on physical-counter-maneuvers such as leg-crossing or squatting and fall avoidance
E. Arrange for an outpatient 72-h Holter monitor

Answer 4
The correct answer is D.

Question 5

A 65 year-old man presents with his second syncopal episode. He notes no warning symptoms prior to his episodes and he had facial trauma following the most recent episode. His initial evaluation consisted of a detailed medical and family history, physical examination, electrocardiogram and echocardiogram.

Which of the following clinical findings noted on initial workup would NOT be an indication for an electrophysiologic study?

A. Abnormal ECG suggesting conduction system disease
B. Abnormal tilt table testing response
C. Syncope during exertion or in supine position
D. Family history of sudden death
E. Evidence of structural heart disease

Answer 5
The correct answer is B.

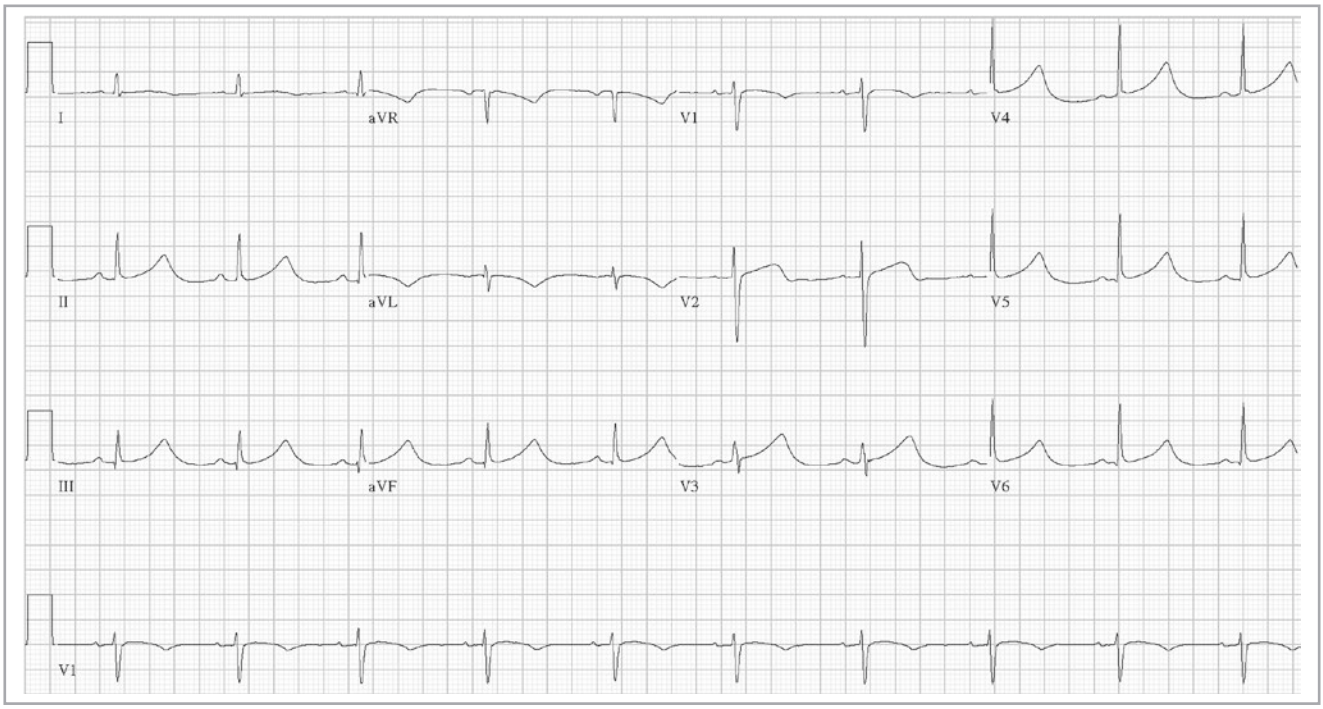

FIGURE 17-7 ECG

Question 6

A 35 year-old woman has a history of 5 prior episodes of syncope over the past 2 years. She occasionally has noted chest pain prior to her syncopal episodes. All of her prior episodes occurred when she was not physically active and mostly while lying in bed. She previously had been referred to a neurologist and had a negative prior neurologic workup including a normal electroencephalogram (EEG). Her family history is notable for a sister who died suddenly at age 25. She denies any other medical problems and any prescription or illicit drug use. On physical exam, her HR was 60, her BP was 115/70 and her cardiac exam reveals no murmurs or extra sounds. Her ECG is seen in Fig. 17-7.

Which of the following is the most likely diagnosis?

A. Hypertrophic cardiomyopathy
B. Brugada Syndrome
C. Arrhythmogenic right ventricular cardiomyopathy
D. Long QT syndrome
E. Wolff-Parkinson-White syndrome

Answer 6

The correct answer is D.

Question 7

Which of the following patients should undergo testing beyond a physical examination and ECG to establish a diagnosis?

A. 40 year-old female who fainted in childhood after seeing blood has syncope while standing in line at the bank
B. 32 year-old male trumpet player who has a syncopal episode while playing a long solo
C. 25 year-old soccer player with no prior evaluation who passes out during a match
D. 28 year-old marathon runner who has prior evaluation revealing structurally normal heart on ECG and echocardiogram who loses consciousness after a race
E. 27 year-old male with pertussis who passes out during a coughing fit.

Answer 7

The correct answer is C.

Question 8

All of the following findings on initial history, physical examination, or electrocardiogram should prompt hospital admission for evaluation except:

A. ECG demonstrating sinus pause of 2 s
B. Physical examination demonstrating elevated jugular venous pressure, rales on lung examination, and lower extremity edema
C. Family history of sudden cardiac death
D. Physical examination demonstrating parvus et tardus, systolic murmur heard best at upper sternal border and absent S2
E. ECG with Right bundle branch block and ST elevations in V1–V3

Answer 8

The correct answer is A.

Explanations to Answers

Question 1

Irrespective of the cardiac arrest at the time of acute myocardial infarction management, implantation of a defibrillator is not indicated in the acute post-myocardial infarction period. The AHA/ACC/HRS guidelines specify that an implantable cardioverter defibrillator is not

indicated within the first 40 days after myocardial infarction. Both the DINAMIT [9] and IRIS [11] trials tested whether implantation of a defibrillator was superior to conventional care in patients with left ventricular dysfunction in the early post-myocardial infarction period. There was no detectable difference in survival between those randomized to ICD and to conventional care in these trials.

Question 2

The patient described likely has idiopathic right ventricular outflow tract tachycardia. This tachycardia is well-tolerated and has an excellent prognosis. Right ventricular outflow tract tachycardia is a cyclic adenosine monophosphate mediated tachycardia, and is typically responsive to calcium channel blockers or beta-blockers, which are often used as first-line therapies. Because of the high success rates and low complication rates associated with catheter ablation for this type of arrhythmia, ablation is a reasonable strategy in patients who do not tolerate these medications, do not wish to take medication, or in whom the medication is unsuccessful.

Question 3

The patient described has a history of myocardial infarction, moderate heart failure symptoms, and severe left ventricular dysfunction with an ejection fraction of 33%. In SCD-HeFT, similar patients that received implantable cardioverter defibrillators had improved survival as compared to those who received either amiodarone or placebo. As such, current guidelines recommend implantation of a defibrillator in those with a left ventricular ejection fraction ≤35%, NYHA class II–III heart failure symptoms, and a prior myocardial infarction.

Question 4

The patient and witness describe an episode of LOC and postural tone with spontaneous recovery consistent with a vasovagal episode. Factors consistent with vasovagal syncope include: standing posture, prodromal symptoms, lack of postictal confusion, and unpleasant environment. She also describes a prior history of benign syncopal episodes as a child also consistent with vasovagal syncope. Her family history, physical exam findings, and ECG also do not raise concern for a cardiac cause of syncope. A low risk young patient with vasovagal syncope can be discharged after careful discussion regarding fall avoidance and education on the importance of hydration and physical counter-maneuvers such as leg crossing with lower body muscle tensing, squatting or arm tensing to raise blood pressure. She has no high risk markers for hospital admission and there is no suspicion of CAD to justify ruling out for MI so option B is incorrect. Given the absence of known SHD and normal ECG and physical exam, an echocardiogram (option A) is unlikely to provide useful additional information. There is little evidence supporting the use of beta-blockers (option C) in vasovagal syncope. Her episodes are so infrequent that a Holter monitor would be unlikely to capture any episodes.

Question 5

The patient gives a history suspicious for syncope due to arrhythmia with lack of a prodrome and syncope causing injury suggesting lack of warning. In one study, male sex, age greater than 54, less than or equal to 2 prior syncopal episodes and less than 5 s of warning prior to syncope were predictive of syncope due to AV block or VT. In patients with concern for syncope due to cardiac arrhythmias, indications for an EP study include: abnormal ECG suggesting conduction system disease (option A), syncope during exertion or in supine position (option C) or with important structural heart disease (option E), family history of sudden death (option D). Class III indications for an EP study include: normal ECG, no known history of SHD and no palpitations. An abnormal tilt table testing response (option B) suggests neurally mediated syncope rather than arrhythmogenic syncope and is not an EP study indication.

Question 6

Several features of this patient's syncopal history are concerning of a cardiac cause of syncope including: syncope while supine and family history of sudden cardiac death. Her ECG demonstrates a prolonged QTc >480 ms. These three factors place her at high risk of long QT syndrome (option D). The remaining answers are incorrect. Hypertrophic cardiomyopathy (option A) usually presents with exertional syncope rather than supine syncope. The ECG in Brugada syndrome (option B) usually demonstrates incomplete or complete right bundle branch block and ST elevations in leads V1–V3. The ECG in Arrhythmogenic Right Ventricular Cardiomyopathy usually demonstrates T wave inversions in leads V2–V4 and an echocardiogram usually reveals right ventricular abnormalities. The ECG in Wolff-Parkinson-White syndrome demonstrates preexcited ventricular complexes.

Question 7

The scenarios described in options A, B, D, and E all involve young individuals with neurally mediated syncope (NMS). Option A is consistent with vasovagal syncope, option B syncope while playing a brass instrument is a form of NMS. Option D describes POST-exertional syncope in an athlete, which is also a form of NMS. It is important to note that the athlete in question, has already had a workup revealing a structurally normal heart, as there should be a high index of suspicion when syncope occurs in athletes. Cough induced syncope (option E) is another example of situational syncope, a form of NMS. Option C describes syncope during exertion, which is a red flag and should be evaluated further.

Question 8

A sinus pause >3–5 s is a concerning ECG abnormality that warrants hospital stay, pauses under 3 s would be unlikely to cause syncope. Option B depicts the physical examination of a patient in congestive heart failure suggesting underlying cardiac etiology and should be admitted for further evaluation. A positive family history of sudden cardiac death is highly concerning in a syncopal patient and supports evaluation in a hospital. Option D describes a patient with severe aortic stenosis, which is a potential cause of syncope and should be further evaluated in a hospital setting. Option E describes a typical ECG in Brugada syndrome and any ECG with evidence of channelopathy should be admitted to the hospital for further workup.

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CHAPTER 18

SARAH V. TSIARAS AND DANIELA R. CROUSILLAT

Systemic Disorders Affecting the Heart

CHAPTER OUTLINE

ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
AF	Atrial fibrillation
ANCA	Antineutrophil cytoplasmic antibodies
aPL	Antiphospholipid
ART	Antiretrovial therapy
AV	Atrioventricular
ANA	Antinuclear antibody
AS	Ankylosing spondylitis
ATTR	Transthyretin amyloid
AL	Immunoglobulin light chain associated amyloid
BB	Beta blocker
CAD	Coronary artery disease
CS	Cardiac sarcoidosis
CT	Computed tomography
CTA	Computed tomography angiography
CVD	Cardiovascular disease
CMP	Cardiomyopathy
ECG	Electrocardiogram
EGPA	Eosinophilic granulomatosis with polyangiitis
EMB	Endomyocardial biopsy
FDG-PET	^{18}Fluoro-2-deoxy-D-glucose positron emission tomography
GCA	Giant cell arteritis
HF	Heart failure
HIV	Human immunodeficiency virus
HTN	Hypertension
KD	Kawasaki disease
LGE	Late gadolinium enhancement
LV	Left ventricle
MD	Muscular dystrophy
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RAIU	Radioactive iodine

RF	Rheumatoid factor
SLE	Systemic lupus erythematous
TA	Takayasu's arteritis
TSH	Thyroid stimulating hormone
TTE	Transthoracic echocardiography

INTRODUCTION

A multitude of systemic diseases can have significant effects on the heart (Table 18-1). Importantly, cardiac manifestations can be the first sign of the underlying systemic disease or represent a complication secondary to the primary systemic disorder. This chapter will focus on the most prevalent systemic autoimmune, inflammatory, infiltrative, infectious, and endocrinological diseases with common cardiac manifestations. These group of diseases are important to recognize as treatment of the underlying disease can often alleviate its cardiovascular manifestations.

INFLAMMATORY ARTHROPATHIES

Rheumatoid Arthritis (RA)

A. **Clinical presentation**

- Women > men, incidence highest 50–70 years old.
- Articular manifestations—symmetric, polyarticular arthritis.
- Extra-articular manifestations—nodules (skin and lung), pleuritis, interstitial lung disease, scleritis.

	Pericarditis / Myocarditis	Cardiomyopathy/ HF	CAD	Conduction disease	Valvular disease	Arrhythmias	Aortic Disease
Hyperthyroidism		Occasional				**Common**	
Alcohol		Occasional				**Common**	
Cocaine	Occasional		**Common**			Occasional	Rare
HIV		Occasional	**Common**				
Lyme	Occasional			**Common**			
RA	Occasional	Occasional	**Common**		Rare		
SLE	**Common**	Occasional	**Common**		Occasional		
Amyloidosis		**Common**		**Common**		**Common**	
GCA			Rare				**Common**
AS				Rare	Rare		
PsA			**Common**				
Sarcoidosis		**Common**		**Common**		**Common**	
Kawasaki			**Common**				
Takayasu's			Occasional				**Common**
Hemochromatosis		**Common**		**Common**			
Still's	**Common**						
EGPA	**Common**	Occasional	Rare				

Common ↕ Rare

TABLE 18-1

SYSTEMIC DISORDERS AFFECTING THE HEART BY PREVALENCE AND CARDIAC MANIFESTATIONS

B. **Cardiac manifestations (60%)**

- Accelerated coronary artery disease (CAD) –2× increased risk of CAD associated with premature morbidity and mortality; reduction in life expectancy by 5–10 years [1].
- Pericarditis and myocarditis—up to 30% (symptomatic in <1%). More common with seropositive, erosive disease.
- Cardiomyopathy(CMP) ± heart failure (HF)—increased risk of ischemic CMP, non-ischemic CMP (amyloidosis, rheumatoid nodule deposition) [2].

C. **Diagnosis**

- Rheumatoid factor (RF; less specific) or anti-cyclic citrullinated peptide antibody (anti-CCP; more specific). Combined sensitivity ~80%.
- Joint erosions on radiographs.
- Cardiac magnetic resonance imaging (MRI) with gadolinium—if clinically suspected myocarditis or to evaluate the etiology of CMP. Ischemic (CAD, prior myocardial infarction) versus non-ischemic pattern of late gadolinium enhancement (LGE) can be seen with inflammation/fibrosis [3].

D. **Treatment**

- CAD—treatment of RA may improve cardiovascular outcomes [4].
- Pericarditis/myocarditis—prednisone 1 mg/kg ± steroid sparing immunomodulator.
- CMP ± HF—treatment of RA + guideline-directed neurohormonal therapies based on LV systolic function.

Systemic Lupus Erythematosus (SLE)

A. **Clinical Presentation**

- Women > men, incidence highest 30–50 years old.
- Skin disease—malar rash, photosensitivity, discoid rash.
- Oral ulcers
- Arthritis—two or more swollen and tender joints.
- Serositis—pleuritis or pericarditis.
- Renal involvement—proteinuria.
- Neurologic involvement—seizures or psychosis.
- Hematologic—leucopenia, thrombocytopenia or hemolytic anemia.
- Antiphospholipid antibody syndrome—arterial or venous thrombosis, thrombocytopenia, second-trimester pregnancy losses.

B. **Cardiac manifestations (50%)**

- Pericarditis—most common cardiac manifestation occurring in 20–50% of patients. Pericardial effusion common, tamponade is rare (<10%) [5].
- CAD—accelerated atherosclerosis and/or coronary vasculitis; increased risk for myocardial infarction and cardiovascular disease (CVD) mortality independent of traditional risk factors [5].
- Valvulitis—inflammatory nodules or nonbacterial, thrombotic valvular vegetations (Libman-Sacks endocarditis) can occur on aortic and/or mitral valves in 3–19% of patients undergoing transthoracic echocardiography (TTE), rarely associated with significant valvular insufficiency. The etiology of Libman-Sacks endocarditis is unknown, but patients with high-titer antiphospholipid (aPL) antibodies may be at higher risk [6].
- Myocarditis—<10% of patients, typically occurs with other disease manifestations.
- CMP ± HF—can be caused by CAD/coronary vasculitis, myocarditis, or hydroxychloroquine (rare but important to exclude).

C. **Diagnosis**

- Clinical diagnosis. Most patients meet 4 of 11 American College of Rheumatology (ACR) 1997 revised classification criteria, which include clinical manifestations (listed above) and the following:
  - Antinuclear antibody (ANA) positivity (>95% of patients).
  - Positive anti-Smith or double-stranded DNA antibody or positive tests for aPL (anticardiolipin antibodies, lupus anticoagulant assay, anti-beta-2 glycoprotein I antibodies)
- Cardiac MRI with gadolinium—if clinically suspected myocarditis or to evaluate the etiology of CMP. Ischemic (CAD, prior myocardial infarction) versus non-ischemic pattern of LGE can be seen with inflammation/fibrosis.
- Endomyocardial biopsy (EMB)-differentiate inflammatory SLE-induced myocarditis from hydroxychloroquine-induced CMP [3, 7].

D. **Treatment**

- Pericarditis—non-steroidal anti-inflammatory drugs (NSAIDs) and low dose corticosteroids if NSAID-refractory.
- Valvulitis—typically clinically silent, anticoagulation recommended for thrombotic events in the setting of Libman-Sacks endocarditis.
- Myocarditis—high dose corticosteroids ± another immunosuppressive agent.
- CMP ± HF-treat SLE, guideline-directed neurohormonal therapies based on LV systolic function, discontinuation of hydroxychloroquine if suspected treatment-induced CMP [3].

Ankylosing Spondylitis (AS)

A. **Clinical presentation**

- Men > women, incidence highest 20–30 years old.
- Axial symptoms—low back/buttock pain due to sacroiliitis (worse with rest).
- Peripheral symptoms—asymmetric lower extremity oligoarthritis and enthesitis.
- Extraarticular symptoms—uveitis, inflammatory bowel disease.

B. **Cardiac manifestations**

- Aortic regurgitation—5–13% of patients, typically mild, asymptomatic.
- Conduction abnormalities—ECG abnormalities in up to 20%, but symptomatic atrioventricular (AV) block rare [8].

C. **Diagnosis**

- Sacroiliitis on radiographs (less sensitive) or MRI (more sensitive).
- Human leukocyte antigen (HLA) B27 positive (90%).
- Screening TTE—not recommended unless clinically indicated.

D. **Treatment**

- Immunosuppression—no role in treating cardiac manifestations.

Psoriatic arthritis (PsA)

A. **Clinical Presentation**

- Equal prevalence among both genders.
- 70% with history of psoriasis, 2–3% risk per year of PsA among patients with known psoriasis. In 10–15%, PsA can precede skin manifestations.
- Clinical manifestations

- Asymmetric polyarthritis (distal interphalangeal (DIP) joints most commonly involved).
- Dactylitis (50%)—diffuse soft tissue swelling with appearance of a "sausage digit."
- Nail lesions (80–90%)-pitting, onycholysis (separation of nail from bed) [9].

B. **Cardiac Manifestations**

- Increased risk of metabolic syndrome, hypertension (HTN), diabetes, and atherosclerosis [10, 11].
- CVD is the leading cause of death (36.2%), 1.3× risk of death compared to general population [12].

C. **Diagnosis**

- Clinical diagnosis—no diagnostic laboratory findings for PsA (10% of patients are seropositive for RF.
- Joint radiographs—characteristic concomitant erosions and new bony formations.

D. **Treatment**

- Based on disease severity, ranging from NSAIDs + non-biologic disease-modifying anti-rheumatic drug (DMARD) to immunomodulators for severe disease.
- Screening and treatment of common atherosclerotic risk factors for risk reduction.

SYSTEMIC VASCULITIDES

Giant Cell Arteritis (GCA)

A. **Clinical manifestations**

- Most common systemic vasculitis, 0.5–1% lifetime risk, occurs in individuals >50 years old.
- Fever, fatigue, weight loss, headache, jaw claudication.
- Vision loss can occur in patients with delayed or no treatment.
- Polymyalgia rheumatica (PMR)-shoulder/hip girdle stiffness and pain present in 40–50%.

B. **Cardiac manifestations**

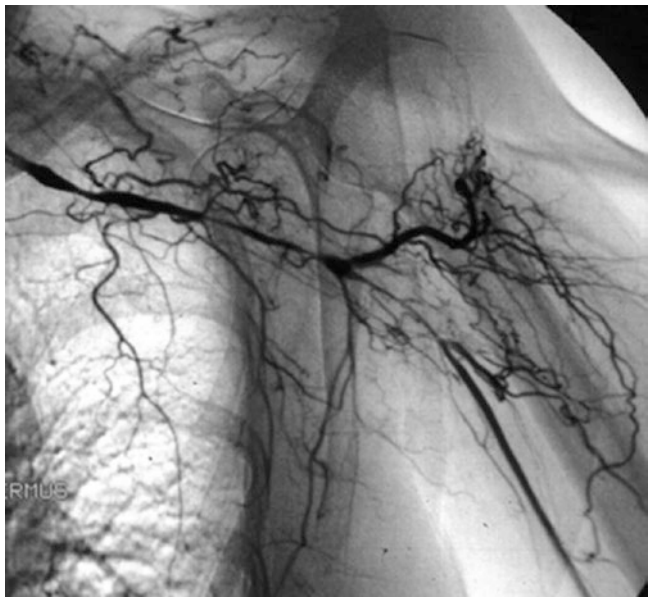
- Large vessel GCA (30–80%)
  - Large vessel vasculitis—involvement of the aorta and major branches, commonly subclavian arteries, leading to symptomatic stenosis (most commonly upper extremity claudication) (Fig. 18-1)
  - Histopathology-inflammation, granulomatous organization, giant cell formation leading to intimal hyperplasia and occlusion.
  - Aortitis—thoracic > abdominal aneurysms, low rates of rupture/dissection [13].

C. **Diagnosis**

- Temporal artery biopsy—granulomatous vasculitis. Temporal artery biopsy negative in ~50% with large vessel GCA.
- Computed tomography angiography (CTA)/magnetic resonance angiography (MRA)—evaluate aorta and large, proximal branches for large-vessel involvement.
- ^{18}Fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET)—evaluate for aortitis/inflammation.
- Erythrocyte sedimentation rate (ESR)—elevated in 96% [14].

FIGURE 18-1

Conventional angiogram from a patient with giant cell arteritis. There are several long, smooth stenoses of the left subclavian artery. Multiple collateral blood vessels are seen in the region of the shoulder. Such a patient will have greatly diminished or absent pulses in the arm but ample blood flow even to the distal extremity because of the collaterals. Re-vascularization attempts are usually not indicated, ineffective, and ill-advised



D. **Treatment**

- Uncomplicated GCA—oral prednisone 1 mg/kg with slow taper for prevention of flares. Effect of glucocorticoid therapy on large vessel GCA has not been studied, unknown if any effect on progression, risk of rupture, or dissection.
- Pulse high dose intravenous steroids—threatened or confirmed visual loss.
- Angioplasty or stenting of subclavian arteries—rarely necessary for ischemic limb symptoms.

Takayasu's Arteritis (TA)

A. **Clinical manifestations**

- Female-to-male ratio 10:1, 90% < 40 years of age. Most prevalent in Asian populations.
- Fever, arthralgias, fatigue, and increased acute phase reactants during the "inflammatory" phase.
- Claudication and long-term complications of large vessel vascular stenosis during the "stenotic" phase.

B. **Cardiac manifestations** [15]

- Vasculitis of large vessels (pan arteritis) and branches leading to inflammation and progressive stenosis, aneurysms, and obliterative stage with vessel occlusion.
  - Limb claudication:
    - Diminished brachial artery pulses, >10 mm Hg difference in systolic blood pressure in upper extremities due to stenosis/near occlusion.
    - Subclavian stenosis leading to arm claudication most common, lower extremity involvement is rare.
  - Coronary ischemia:
    - Ostial narrowing due to coronary vasculitis, fistulas and coronary aneurysms less common.

- HTN:
  - Narrowing of one or both renal arteries, reduction in elasticity of aorta and branches.
  - Difficult to formally assess secondary to peripheral artery involvement rendering noninvasive blood pressure monitoring challenging.
- Central nervous system manifestations:
  - Involvement of carotid or vertebral arteries causing lightheadedness, vertigo, visual impairment.
- Pulmonary artery stenosis (50%)—may cause pulmonary HTN, symptoms uncommon.
- Aortic insufficiency due to aortic root dilation (20%).

C. **Diagnosis**

- Histologically similar in appearance to GCA (see above).
- Vascular imaging (CTA/MRA)—narrowing and occlusion of large arteries not explained by other causes (such as fibromuscular dysplasia, Ehlers-Danlos syndrome or segmental arterial mediolysis).
- Catheter-based angiography—measure core aortic pressure, assess gradients across peripheral stenosis; coronary angiography for suspected coronary ischemia.

D. **Treatment**

- Prednisone 1 mg/kg + ~50% require addition of another immunomodulator.
- Angioplasty or surgical bypass grafting may be required for irreversible severe stenosis.

Kawasaki Disease (KD)

A. **Clinical manifestations**

- Medium vessel childhood vasculitis affecting mainly coronary arteries; rare in adults.
- Initial respiratory or gastrointestinal illness is typically self-limited (1–2 weeks). Fever, mucositis (strawberry tongue), bilateral conjunctivitis, erythematous rash on hands and feet, cervical lymphadenopathy.
- Subacute phase—coronary artery dilation, aneurysms.

B. **Cardiac manifestations**

- Coronary artery aneurysms (25%)—most common in proximal left anterior descending artery (LAD) and right coronary artery (RCA). Risk factors include delayed diagnosis, young age (<6 months), male sex.
  - Most aneurysms peak in size in 4–6 weeks, approximately 50–75% regress within 2 years after initial illness.
  - Persistent aneurysmal segments are prone to tortuosity and thrombosis in adult life leading to myocardial ischemia.
- Less common cardiac manifestations include mitral regurgitation due to valvulitis, depressed myocardial contractility in the acute inflammatory setting.
- Long term complications (adults):
  - Accelerated atherosclerosis—highest risk in patients with persistent aneurysms. Complications include myocardial infarction (leading cause of death), and arrythmias [16].

C. **Diagnosis**

- Clinical diagnosis
- TTE—asses for proximal coronary artery aneurysms (children), non-invasive imaging (CTA/MRA) can also be used to image entire coronary tree.
- Persistent aneurysms (adults)—serial nuclear stress testing to evaluate for inducible ischemia; coronary angiography.

D. **Treatment**

- Children—low-dose aspirin for 4–6 weeks, discontinued if no coronary involvement. Treatment with intravenous immune globulin (IVIG) helps prevent cardiac complications. The benefit of corticosteroids is unproven.
- Adults—aspirin + systemic anti-coagulation for persistent medium to large (>8 mm) aneurysms.

Eosinophilic Granulomatosis with Polyangiitis (EGPA), Formerly Churg Strauss Syndrome

A. **Clinical manifestations**

- Antineutrophil cytoplasmic antibodies (ANCA)-associated small vessel vasculitis
- Clinical triad-Asthma, allergic rhinitis, peripheral eosinophilia (Fig. 18-2).

B. **Cardiac manifestations** [16]

- Cardiac abnormalities—most common cause of morbidity and mortality, affecting 40–60% of patients. Associated with higher peripheral eosinophilic counts, inversely associated with ANCA positivity [17].
- CMP ± HF (major cause of morbidity and mortality):
  - Eosinophilic endomyocarditis (poor prognosis)
- Three phases: acute myocardial necrosis, microvascular fibrin deposition and thrombus formation and myocardial fibrosis.
  - Coronary artery vasculitis (rare, <1%).
  - Pericardial effusions (40%), frequently asymptomatic.

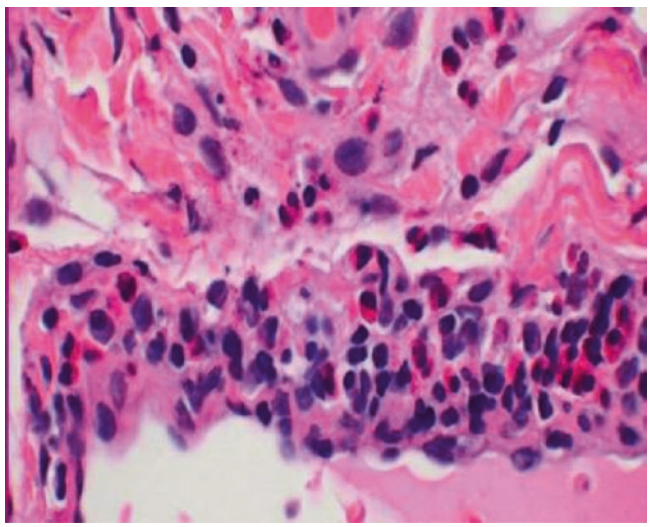


FIGURE 18-2

Skin biopsy from a patient with eosinophilic granulomatosis with polyangiitis (EGPA) syndrome who presented with focal areas of palpable purpura and ulceration on the lower extremities. The biopsy demonstrates extensive eosinophilic infiltration of the blood vessel wall

C. **Diagnosis**

- Peripheral eosinophilia.
- Positive ANCA antibodies (~50%)-less common in patients with cardiac involvement.
- Tissue biopsy (small to medium vessel vasculitis).
- Cardiac MRI with gadolinium, EMB if endomyocarditis suspected.

D. **Treatment**

- Significant cardiac involvement—high-dose corticosteroids and cyclophosphamide. Rituximab may be useful if corticosteroid or cyclophosphamide refractory.
- Anticoagulation indicated for presence of LV thrombi.

AUTOIMMUNE DISEASES

Systemic Sclerosis (Scleroderma)

A. **Clinical presentation**

- Women > men, incidence highest 30–50 years old.
- Diffuse form—skin thickening involving trunk, face and extremities. Raynaud's phenomenon, interstitial lung disease, renal and gastrointestinal dysmotility.
- Limited form (**CREST** syndrome)—Skin thickening limited to extremities. **C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia.

B. **Cardiac manifestations**

- Pulmonary HTN—most common in limited disease (8–20%).
- Conduction disease—ECG abnormalities in 25–75%, but symptomatic AV block is rare (<2%).
- Diastolic dysfunction—~30% due to myocardial fibrosis.
- Pericarditis—clinically significant pericarditis is uncommon (0–15%).

C. **Diagnosis**

- Skin thickening in the proper clinical setting.
- Diffuse form—positive ANA, anti-topoisomerase 3 (Scl-70) antibody present in 30%.
- Limited form—positive ANA, anti-centromere antibody (ACA) present in 70–80%.

D. **Treatment**

- Symptomatic treatment only. Immunomodulatory agents are unlikely to benefit cardiac manifestations.

Adult Onset Still's Disease

A. **Clinical manifestations**

- Disease onset typically 16–35 years old.
- Cyclic (quotidian) fever, salmon-colored rash with fevers, arthritis, hepatitis and serositis [18].

B. **Cardiac manifestations**

- Pericarditis—25% of patients [8].

C. **Diagnosis**

- Clinical diagnosis.
- Laboratory abnormalities—markedly elevated ferritin (70%), elevated hepatic aminotransferases (75%).

D. **Treatment**

- Prednisone 1 mg/kg.
- Interleukin-1 receptor or interleukin-6 receptor blockade if refractory to prednisone.

Immunoglobulin G4-Related Disease (IgG4-RD)

A. **Clinical manifestations** [19]

- Infiltrative immune-mediated systemic disease with single or multi organ involvement with four main clinical phenotypes:
  - Pancreato-hepato-biliary disease
  - Retroperitoneal fibrosis and/or non-infectious aortitis
  - Head-and-neck limited disease
  - Classic Mikulicz syndrome (dacryoadenitis, sialadenitis)
- Emerging recognition as unifying disease entity; mimicker of many inflammatory, autoimmune, malignant, and infectious disorders.
- Pathogenesis incompletely understood.
- Presents with subacute symptoms related to specific organ involvement:
  - Mass or enlargement of affected organ
  - Lymphadenopathy
  - Atopy (i.e. asthma, allergic rhinitis) (40%)

B. **Cardiac manifestations**

- Inflammatory, non-infectious aortitis/periaortitis
- Thoracic and abdominal aortic aneurysms
- Aortic dissection

C. **Diagnosis**

- Serum IgG4 levels—elevated in 2/3 of patients.
- Histopathology is gold standard for the diagnosis with three central features:
  - Lymphoplasmacytic infiltration of IgG4 positive plasma cells
  - Storiform fibrosis
  - Obliterative phlebitis.

D. **Treatment** [20]

- Systemic glucocorticoids (i.e. prednisone 0.6 mg/kg/day) for inflammatory stage and remission induction therapy.
- Immunosuppressive, steroid sparing therapies for refractory disease. No randomized controlled trials, but case series with benefit from B-cell depleting therapies (i.e. rituximab).

INFILTRATIVE DISEASES

Cardiac Sarcoidosis (CS)

A. **Clinical presentation**

- Multisystem granulomatous disorder of unknown etiology.
- Incidence highest 20–40 years old, more common among African Americans.

- Classic findings—bilateral hilar adenopathy, pulmonary infiltrates, skin, joint, eye lesions.
- Cardiac involvement (5%)—20–25% with asymptomatic cardiac involvement.
- Cardiac sarcoidosis triad—conduction abnormalities, ventricular arrythmias, and HF. LV dysfunction is most important predictor of prognosis [21].

B. **Cardiac manifestations**

- AV block (20–50%)—most common cardiac manifestation.
- Ventricular arrhythmias (30%)—high risk of sudden cardiac death.
- CMP ± HF—dilated or restrictive CMP most common, right ventricular involvement possible.

C. **Diagnosis**

- Chest radiograph/chest computed tomography (CT)—bilateral hilar adenopathy.
- Tissue biopsy—non-caseating granulomas and multi-nucleated giant cells. EMB seldom indicated (positive in <25% with CS) due to patchy, focal nature of disease (Fig. 18-3).
- ECG—fascicular or bundle branch block (right bundle branch block more common).
- Serum angiotensin converting enzyme (ACE)—poor sensitivity/specificity.
- TTE—thickened myocardium, basal septal thinning, LV systolic and diastolic dysfunction, regional wall motion abnormalities in non-coronary distribution.
- Cardiac MRI—LGE in basal segments particularly septum and lateral wall with sparing of the endocardium.
- FDG-PET-identifies active inflammation; useful disease activity marker.

D. **Treatment**

- Prednisone 1 mg/kg with taper based on clinical disease activity and serial FDG PET scans.
- Refractory disease—methotrexate and/or anti-tumor necrosis factor (TNF) agents.
- Implantable cardioverter-defibrillator (ICD) recommended with spontaneous ventricular arrythmias, prior cardiac arrest, and LV systolic function <35% despite optimal medical therapy [21].

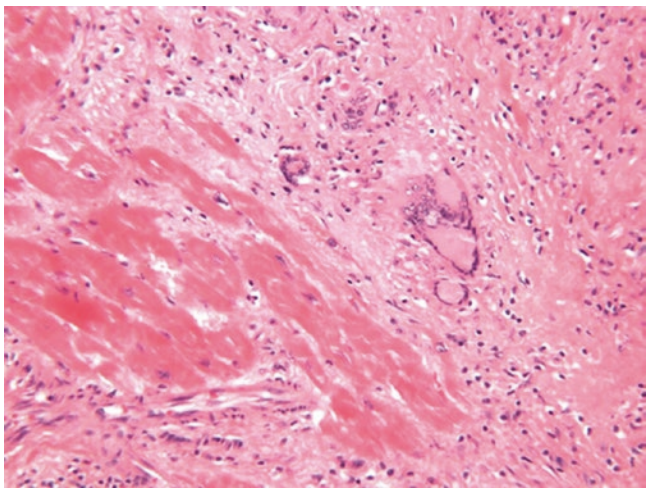


FIGURE 18-3

Granulomatous inflammation within the myocardium of a patient with sarcoidosis. Several multinucleated giant cells without caseating features are shown

Hemochromatosis [22]

A. **Clinical presentation**

- Autosomal recessive hereditary disorder of systemic iron overload, commonly mutations in *HFE* (human hemochromatosis protein) gene.
- Secondary causes—hereditary anemias/malignancy, transfusion dependence.
- Symptoms at age 40 in males, later in females due to iron loss associated with menses, pregnancy.
- Classic signs—liver disease, diabetes mellitus, arthropathy, skin hyperpigmentation, lethargy, impotence.

B. **Cardiac Manifestations**

- Dilated CMP ± HF—restrictive physiology and impaired diastolic function, progressive LV dilation.
- Conduction abnormalities—iron deposition within myocardium.

C. **Diagnosis**

- Transferrin saturation >45%.
- Serum ferritin (>200 ng/mL males, >150 ng/mL females).
- C282Y, H63D mutation analysis—homozygous C282Y mutation at highest risk.
- TTE—impaired diastolic dysfunction (restrictive filling pattern), restrictive and dilated CMP variants.
- Cardiac MRI—quantification of myocardial iron overload via measurement of T2* relaxation times.
- EMB—poor sensitivity/specificity due to heterogeneous nature of iron deposition.

D. **Treatment**

- Phlebotomy ± iron chelation therapy—may be associated with reversal of LV dysfunction. Poor prognosis without treatment.

Amyloidosis [22, 23]

A. **Clinical presentation**

- Inappropriate deposition of insoluble amyloid fibrils in the heart and other organs.
- Amyloid subtypes with cardiac deposition:
  - Immunoglobulin light chain associated amyloid (AL)-plasma cell dyscrasia with or without multiple myeloma.
  - Transthyretin amyloid (ATTR)—hereditary or "wild-type"/senile systemic amyloidosis. Val122Ile mutation common among African/Caribbean descent.
- HF, nephrotic syndrome (AL subtype), peripheral/autonomic neuropathy, conduction heart disease, macroglossia, carpal tunnel, periorbital purpura.

B. **Cardiac Manifestations**

- Infiltrative, restrictive CMP ± HF.
- Conduction heart disease.
- Atrial and ventricular arrythmias.

C. **Diagnosis**

- Screen for plasma cell dyscrasia—serum free light chains, serum/urine electrophoresis with immunofixation.
- Positive tissue biopsy—fat pad aspirate/biopsy, bone marrow biopsy. Consider EMB (very sensitive) if other diagnostic testing is negative/equivocal. A tissue biopsy is required for the diagnosis of AL amyloid.

- ECG—low voltage, pseudo infarction pattern.
- TTE—right and LV myocardial thickening, valvular thickening, biatrial enlargement, pericardial effusion.
- 99^{m}-Tc pyrophosphate (PYP) scan:
  - Negative/mild uptake: AL amyloid.
  - Positive uptake: ATTR amyloid.
- Cardiac MRI—subendocardial LGE.

D. **Treatment**

- AL amyloid—worse prognosis than ATTR if untreated (25% mortality at 12 months). Chemotherapy ± autologous stem cell transplant.
- ATTR amyloid-Conventional HF therapies poorly tolerated. Liver transplant for mutant ATTR (produced in liver). Tafamadis is now approved for use and investigational trials for targeted therapies ongoing.

ENDOCRINOPATHIES

Hyperthyroidism

A. **Clinical presentation**

- Weight loss, tremors, insomnia, heat intolerance, warm moist skin, hyperreflexia, hyper defecation. Goiter may be present. Proptosis may occur in Graves' disease.
- Thyroid storm—fever, sweating, marked tachycardia, arrhythmias, pulmonary edema, high-output congestive HF, tremulousness, delirium, psychosis, abdominal pain, jaundice.

B. **Cardiac manifestations**

- ↑ sympathetic tone (tachycardia, palpitations, atrial fibrillation [AF]), ↑ cardiac output [CO] (from ↑ heart rate [HR], in severe cases ↑ stroke volume [SV]), ↑ inotropy, ↑ circulatory demand from hypermetabolism, ↓ peripheral vascular resistance (PVR), ↑ pulse pressure.
- Arrhythmia: 5–15% of patients will have AF.

C. **Diagnosis**

- ↓ Thyroid stimulating hormone (TSH), ↑ thyroid hormones (free thyroxine [T4] and/or triiodothyronine [T3]); ↑ thyroid antibodies in Graves' disease.
- Radioactive iodine (RAI) uptake/thyroid scan:
  - ↑ RAI uptake (thyroid scan pattern)-Graves' disease (homogeneous), toxic multinodular goiter (heterogeneous), toxic adenoma (focal), TSH-secreting pituitary tumors (homogenous).
  - ↓ RAI uptake—iodide-induced thyrotoxicosis, thyroiditis (autoimmune, pos-viral/subacute, drug induced [amiodarone, lithium, interferon-alpha, interleukin-2, granulocyte macrophage colony-stimulating factor]), exogenous thyroid hormone ingestion, struma ovarii.

D. **Treatment**

- Methimazole ± inorganic iodine (after methimazole) to ↓ release of preformed thyroid hormone (Wolff-Chaikoff effect), ±glucocorticoids (↓T4 to T3 conversion).
- If refractory-RAI ablation, thyroidectomy.
- Thyroid storm—propylthiouracil (PTU), super-saturated potassium iodide (SSKI) after PTU, dexamethasone. ±beta-blocker (BB) depending on cardiac state.

- AF
  - BBs (preferably propranolol, atenolol, or metoprolol which also ↓T4 to T3 conversion) non-dihydropyridine calcium channel blocker if BB contra-indicated.
  - Anticoagulation for thromboembolism prophylaxis based on traditional stroke risk factors.
  - Strategies to maintain normal sinus rhythm (i.e. cardioversion) should be deferred until euthyroid state is achieved [24].

Amiodarone-Induced Thyroid Disease

A. **Clinical presentation**

- Iodine content (37%) of amiodarone can precipitate hypo or hyperthyroidism, thyroiditis, and/or autoimmune thyroiditis (Grave's/Hashimoto's) due to cytotoxic effects.

B. **Cardiac manifestations**

- Signs and symptoms of hyperthyroidism (as above) or hypothyroidism (hair loss, fatigue, weight gain, dry/coarse skin).

C. **Diagnosis**

- Screening thyroid function tests every 3 months.
- If TSH >10—amiodarone-induced hypothyroidism.
- If TSH <0.1—amiodarone-induced thyrotoxicosis (AIT).

D. **Treatment**

- Amiodarone induced hypothyroidism—Start thyroid hormone replacement (25–50 mcg/day) and titrate up every 6 weeks until TSH normalizes.
- Amiodarone induced thyrotoxicosis (AIT)—methimazole ± glucocorticoids.
- If refractory to medical therapy, consider thyroidectomy.
- Discontinuation of amiodarone has not been shown to improve clinical outcomes [25].

SECONDARY CAUSES OF HYPERTENSION (TABLE 18-2)

Pheochromocytoma/Paraganglioma

A. **Clinical presentation**

- Rare catecholamine-secreting tumors, estimated incidence 1/125,000 per year, <0.2% of HTN patients.

B. **Cardiac manifestations**

- HTN, paroxysmal palpitations, early morning orthostatic hypotension.
- CMP—secondary to catecholamine excess/tachycardia.

TABLE 18-2

SECONDARY CAUSES OF HYPERTENSION

DISORDERS ASSOCIATED WITH NORMAL K+	DISORDERS ASSOCIATED WITH LOW K+
Hyperthyroidism	Primary aldosteronism
Pheochromocytoma/paraganglioma	Cushing's syndrome
Acromegaly	Congenital adrenal hyperplasia

C. **Diagnosis**

- Screening plasma metanephrine levels (sensitivity 96–100%, specificity 85–89%).
- 24-h urine catecholamine and metanephrine levels (±dopamine).
- CT/MR for localization of tumor if laboratory work up positive.

D. **Treatment**

- Surgical resection
- Peri-operative management:
  - Alpha blockade (i.e. phenoxybenzamine or doxazosin) 7–10 days prior to surgery, high sodium diet (>5 gm/day) and aggressive volume repletion to control orthostasis.
  - Add BB (i.e. propanolol) once α-blockade at goal to control tachycardia.

Primary Aldosteronism

A. **Clinical presentation**

- Hypokalemia, mild hypernatremia, adrenal incidentaloma, polyuria/nocturia, periodic paralysis (Asians).
- Aldosterone-producing adenoma (25%), primary adrenal hyperplasia (2%).

B. **Cardiac manifestations**

- HTN at age <30 (accounts for 5% of early onset HTN).
- Resistant or moderate/severe HTN (≥3 drugs with poor control).

C. **Diagnosis**

- Positive screening test—Plasma aldosterone concentration (PAC) ≥15 ng/dL and PAC/plasma renin activity (PRA) ratio ≥20 (with PRA usually <1.0 ng/mL/h). For accuracy, testing must be performed off aldosterone receptor antagonists.
- If screening laboratory tests positive—confirmatory saline suppression test followed by dedicated adrenal imaging and/or consideration of adrenal venous sampling.

D. **Treatment**

- Surgery for unilateral or ectopic disease.
- Medical management (mineralocorticoid receptor blockade, low sodium diet) for bilateral disease and certain cases of familial hyperaldosteronism.

Cushing's Syndrome/Hypercortisolism

A. **Clinical presentation**

- Excess cortisol caused by excess adrenocorticotropic (ACTH) secretion (65% ACTH producing adenoma, 10% ectopic ACTH); 25% adrenal adenoma.
- Easy bruising, weight gain, proximal muscle weakness, wide striae, hirsutism, facial plethora, hypokalemia.

B. **Cardiac manifestations**

- Increased risk for CVD morbidity/mortality, accelerated atherosclerosis, LV hypertrophy, impaired contractility, dilated CMP, increased risk of thromboembolic events.
- Secondary cause of HTN.
- Carney complex—triad of hypercortisolism (micronodular adrenal lesions), cardiac myxoma, and pigmented dermal lesions (monogenic autosomal dominant disorder due to mutations in *PKAR1A* tumor suppressor gene) [26].

C. **Diagnosis**

- Elevated 24-h urine free cortisol collection or midnight salivary cortisol ×2
- Overnight 1 mg dexamethasone suppression test with 8 AM serum cortisol >1.8 mcg/dL.

D. **Treatment**

- Surgical resection—(pituitary surgery, adrenalectomy, resection of carcinoid/tumor).
- Medical treatment—(ketoconazole, metyrapone, octreotide, pasireotide, cabergoline, mifepristone) ± radiation therapy.

Acromegaly [27]

A. **Clinical presentation**

- Growth hormone excess from hyperfunctioning pituitary adenoma.
- Enlarging hands/feet/head, coarsening of facial features, frontal skull bossing, arthralgias/arthritis, carpal tunnel, prognathism, sleep apnea, skin tags, hyperhidrosis, visceromegaly, tumor mass effects (headaches, vision changes, cranial nerve palsy).

B. **Cardiac manifestations**

- Short term (<5 years)—increased LV mass index, increased systemic vascular resistance.
- Untreated—HTN, cardiac hypertrophy → global LV diastolic dysfunction/LV hypertrophy, CMP, CHF.
- 4× increased risk of complex ventricular arrythmias.
- 20% symptomatic heart disease, CVD accounts for 60% of deaths.

C. **Diagnosis**

- Elevated insulin-like growth factor (IGF-1) levels or growth hormone nadir >1 mcg/L after oral glucose tolerance test (OGTT).

D. **Treatment**

- Medical therapy—dopamine agonists, somatostatin receptor ligands, or growth hormone receptor antagonists.
- Surgical resection of pituitary tumor ± radiation therapy.

INFECTIONS/TOXINS

Lyme Disease

A. **Clinical presentation**

- Early localized disease—erythema migrans rash, arthralgias (without joint effusions) and constitutional symptoms.
- Early disseminated disease—cranial neuropathies, meningitis and peripheral neuropathy.
- Late disseminated disease—large joint arthritis (with effusions), encephalopathy, peripheral neuropathy.

B. **Cardiac manifestations**—occur in early disseminated disease (1–2 months after the onset of symptoms) in 1.5–10% of untreated patients [28].

- AV block of varying severity—most common cardiac manifestation, present in 20–50% of patients.
- Myopericarditis—self-limited, mild. May be present but tends to be relatively mild with <15% of patients demonstrating signs of HF and only mild LV systolic dysfunction.

C. **Diagnosis**

- Lyme antibody confirmed by Western blot.
- ECG, ambulatory cardiac monitor in patients with suspected carditis.

D. **Treatment**

- Appropriate treatment for early features of localized Lyme disease can prevent subsequent Lyme carditis.
- Mild manifestations
  - 1st degree AV block (PR interval <300 ms).
  - Oral doxycycline for 21 days.
- Severe manifestations
  - 2nd or 3rd degree AV block, first degree AV block with PR interval >300 ms, and/or symptoms.
  - Recommended hospitalization for telemetry monitoring with consideration of a temporary pacemaker for symptomatic, high degree AV block.
  - Intravenous ceftriaxone until resolution of high degree AV block with transition to oral antibiotics to complete 28 days of therapy [29].
- Good prognosis-self-limited with treatment with resolution of AV block within days to weeks. No indication for a permanent pacemaker.

Human Immunodeficiency Virus (HIV)

A. **Clinical presentation**

- CVD is primary cause of morbidity and mortality among HIV-infected individuals.
- Antiretroviral therapy (ART) is linked to increased risk of HTN, hyperlipidemia, and metabolic syndrome.

B. **Cardiac manifestations**

- Accelerated atherosclerosis-multifactorial due to chronic inflammation from virus itself, burden of traditional risk factors (i.e. tobacco use), non-traditional risk factors (i.e. substance use, hepatitis C), and side effects of antiretroviral therapy (ART) [30].
- Dyslipidemia—HIV virus itself, hypertriglyceridemia common with ART.
- HIV CMP—etiology not known, typically asymptomatic, most commonly associated with diastolic dysfunction, LV dysfunction more common in untreated HIV-infected.
- Myocarditis, pericarditis—uncommon in era of ART.

C. **Diagnosis**

- Echocardiography for suspected CMP ± HF.
- CVD risk screening tests (lipids, hemoglobin A1c)

D. **Treatment**

- Timely treatment of HIV infection.
- Cardiovascular risk assessment and risk factor modification (smoking cessation, aggressive treatment of dyslipidemia).
- Treatment of HIV + guideline-directed neurohormonal therapies if LV systolic function.

Cocaine Use Disorder

A. **Clinical presentation**

- Acute effects—increased sympathomimetic stimulation (increased inotropy, heart rate, systemic blood pressure, coronary artery constriction), pro-thrombotic, pro-arrhythmic.

- Chest pain, back pain, palpitations, altered mental status.

B. **Cardiac Manifestations**

- Myocardial ischemia/infarction (most common)—increased myocardial demand, vasoconstriction/spasm, in-situ thrombosis.
- Myocarditis/dilated CMP—catecholamine—induced toxicity.
- Arrythmias (less common).
- Extra-cardiac—Aortic dissection, stroke.

C. **Diagnosis**

- Serum/urine toxicology—cocaine metabolites.
- Serial serum biomarkers (troponin T).
- Consider CTA if aortic dissection suspected.

D. **Treatment**

- Similar medical management to acute coronary syndrome caused by other etiology except for BBs (not recommended in the acute management due to unopposed alpha stimulation) [31].
- Benzodiazepines—decrease sympathetic tone.

Alcohol Use Disorder

A. **Clinical presentation**

- History of moderate to daily alcohol use (>80 g per day over a period of at least 5 years).

B. **Cardiac Manifestations**

- Atrial arrythmia—higher incidence of AF.
- Acquired dilated CMP ± HF—associated with chronic use; typically, reversible with cessation.

C. **Diagnosis**

- TTE—LV dilation and dysfunction.

D. **Treatment**

- Abstinence from alcohol.
- Guideline-directed neurohormonal therapies based on LV systolic function.

Medication Induced Valvular Heart Disease

A. **Clinical Presentation**

- Pathogenesis—increased serotonin activity leads to fibroblast growth and fibrogenesis which causes leaflet thickening/tethering leading to valvular regurgitation; similar to carcinoid induced valvular disease.
- Drugs implicated:
  - Ergotamine—used for migraine treatment or prevention.
  - Cabergoline—dopamine agonist for hyperprolactinemia and previously used in Parkinson's.
  - Fenfluramine/phentermine ("fen-phen")—diet pill, withdrawn from market

B. **Cardiac Manifestations**

- Asymptomatic valvular heart disease (regurgitation most common)
- Heart failure

C. **Diagnosis**

- Auscultation of new or pathologic murmur with evidence of VHD by TTE.
- Surveillance TTE not recommended.

D. **Treatment**

- Drug cessation

OTHER SYSTEMIC DISEASES

Cirrhosis

A. **Clinical presentation**

- Cardiac manifestations most common with decompensated, end stage liver disease.
- Hyperdynamic syndrome-↑HR, ↑CO, ↓ systemic vascular resistance, ↓BP due peripheral and splanchnic vasodilation.

B. **Cardiac Manifestations**

- Cirrhotic CMP ± HF—diastolic dysfunction and impaired contractile reserve most common, LV dysfunction rare except with alcoholic cirrhosis.
- QTc prolongation (60%)
- Asymptomatic CAD
- Portopulmonary HTN (POPH)—pulmonary arterial HTN in the setting of portal HTN; severity does not correlate with degree of cirrhosis or liver dysfunction [32].

C. **Diagnosis**

- Echocardiography for suspected CMP ± HF.
- Right heart catheterization—evaluate for pulmonary arterial HTN.
- CVD screening—prior to liver transplantation.

D. **Treatment**

- Treatmentof underlying cause of liver cirrhosis (i.e. hepatitis C).
- Consideration of liver transplantation.

Muscular Dystrophy (MD)

A. **Clinical Presentation**

- X-linked condition caused by mutation in the dystrophin gene.
- **Duchenne**—presents age 2–3 with proximal then distal skeletal muscle weakness.
- **Becker**—milder and presents later.

B. **Cardiac Manifestations**

- Atrial and ventricular arrythmias
- Conduction abnormalities (atrial level and AV node)
- Heart failure

C. **Diagnosis**

- Elevated creatine phosphokinase (CPK)
- ECG—tall right precordial R waves with an increased R/S ratio and deep Q waves in leads I, aVL, and V5-6.
- TTE—dilated CMP with extensive fibrosis of the posterobasal left ventricular wall, right ventricular involvement precedes LV involvement with Becker MD.

D. **Treatment**

- Screening—annual EKG and echocardiogram in affected boys. Female carriers should have screening cardiac MRI in early adulthood [32].
- Angiotensin converting enzyme (ACE) inhibitor should be initiated early in life (by age 10).
- Treatment of AV block
  - Permanent pacemaker
    - Class I indication for pacemaker with third degree or second degree AV block at any anatomic level.
    - Pacemaker may be considered for first degree AV block or any fascicular block [33].

REVIEW QUESTIONS

1. 35-year-old man with chronic low back pain is referred by his primary care physician for an evaluation of a murmur. Physical examination reveals a heart rate of 80 beats per minute (bpm) and blood pressure 116/74 mmHg. A II/IV early diastolic murmur with a blowing, decrescendo quality is heard over the left lower sternal border. There are no gallops. There is no joint pain, laxity or swelling. Examination of the back reveals loss of the normal lumbar lordosis and tenderness of both sacroiliac joints. The erythrocyte sedimentation rate is 28 mm/h (normal <15). Complete blood count and chemistry profile are unremarkable. Which of the following is likely to confirm the diagnosis?

A. Blood cultures
B. HLA-B27 testing
C. Ambulatory blood pressure monitoring
D. Slit lamp eye exam
E. Fluorescent treponemal antibody testing

B—Chronic back pain with bilateral sacroiliac tenderness in a young man raises suspicion for ankylosing spondylitis (AS). Aortic regurgitation is seen in up to 13% of patients with AS. 90% of patients with AS are HLA-B27 positive. Sacroiliitis on plain film or MRI would also be suggestive AS.

2. A 66-year-old man with a history of asthma presents to the Emergency Department with dyspnea. His temperature is 100.8°F, pulse is 110 bpm, blood pressure 106/48 mmHg, and oxygen saturation 98% on 4 L nasal cannula. Examination reveals a jugular venous pressure of 11cm, bibasilar crackles, a purpuric rash on both lower extremities, and decreased sensation in the right hand up to the wrist. Laboratory evaluation is as follows:

WBC	9.4 th/cmm
Hgb	10 g/dL
Hct	30.6%
Platelets	468 th/cmm
Neutrophils	55%
Lymphocytes	20%
Eosinophils	25%
Monoctyes	0%
Basophils	0%
Sodium	140 mmol/L
Potassium	4.2 mmol/L
Chloride	106 mmol/L
Carbon Dioxide	24 mmol/L
BUN	38 mg/dL
Creatinine	1.7 mg/dL

Urinalysis—3+ blood, 2+ protein, nitrite and leukocyte esterase negative

What diagnostic test is most likely to confirm the diagnosis?

A. TTE
B. Cardiac catheterization with myocardial biopsy
C. ANCA testing
D. Skin biopsy
E. Nerve conduction studies

D—This patient's heart failure is likely due to myocarditis from eosinophilic granulomatosis with polyangiitis as evidence by petechial rash, neurologic findings, renal disease, eosinophilia and history of asthma. Anti-neutrophil cytoplasmic antibodies (ANCA) are positive in some patients with EGPA, but less than 50% in some series. A skin biopsy of the purpuric lesions would demonstrate leukocytoclastic vasculitis with intensive eosinophil infiltration confirming the diagnosis.

3. 67-year-old woman with a history of HTN and hyperlipidemia presents with right arm pain. Over the past several months she has experienced arm pain with activity that resolves with rest. She denies chest pain and shortness of breath. She has also noticed headaches and bilateral hip pain. Examination reveals temperature 99.2°F, pulse 68 bpm, and blood pressure 95/66 on the right arm and 130/68 on the left arm. Cardiac examination is unremarkable. No bruits are audible. Radial and brachial pulses are absent on the right. Erythrocyte sedimentation rate is 68 mm/h. Angiography reveals stenosis of the right subclavian artery and a 3.5 cm thoracic aortic aneurysm. Which of the following is the most likely diagnosis?

A. Atherosclerosis
B. Takayasu's arteritis
C. Segmental arterial mediolysis
D. Giant cell arteritis
E. Ehlers-Danlos syndrome

D—Headaches, hip pain and elevated inflammatory markers in a patient older than 50 years of age is suggestive of giant cell arteritis (GCA) which can lead to large vessel vasculitis in up to 20% of patients with the disease. Takayasu's arteritis, which can

cause a similar large vessel vasculitis to GCA, is made less likely by the patient's age.

4. 45-year-old female with a history of gastroesophageal reflux disease and constipation presents to the Emergency Department with dyspnea. Heart rate is 95 bpm, blood pressure 145/76 and oxygen saturation 94% on 2 L nasal cannula. Examination reveals jugular venous pressure of 12 cm, an S4 gallop, bibasilar crackles and thickened skin over both hands, extending up to the elbows. There is also tight skin over her chest and abdomen. The patient is unable to close her hands completely. Laboratories reveal troponin I 0.1 (ref <0.06). ECG demonstrates LV hypertrophy and t-wave inversions in leads II, III, V4 and V5. What is the likely etiology of her heart failure?
   A. Acute coronary syndrome
   B. HTN
   C. Myocardial fibrosis
   D. Myocarditis
   E. Constrictive pericarditis

   C—This patient is likely suffering from scleroderma as evidenced by skin thickening and gastrointestinal dysmotility. Diastolic dysfunction is a well-described manifestation of scleroderma and occurs most commonly due to myocardial fibrosis.

5. A 30-year-old man is referred for HTN, not currently on treatment. The patient is a non-smoker, non-drinker and there is no family history of HTN. Physical examination was significant for a blood pressure of 161/96, BMI 24, and otherwise normal. Lab studies: Na = 140 mEq/L, K = 3.5 mEq/L, Cr = 0.8 mg/dL, PAC (plasma aldosterone concentration) = 35 ng/dL, PRA (plasma renin concentration) = 0.8 ng/mL/h. What is the next step?
   A. Order a magnetic resonance angiogram of the renal arteries
   B. Order a CT scan of the adrenal glands
   C. Schedule adrenal venous sampling for aldosterone
   D. Start spironolactone
   E. Perform a saline suppression test

   E—The patient has early onset HTN with normokalemia. His PAC is elevated, PRA is suppressed, and PAC/PRA ratio is >20, consistent with primary aldosteronism. Confirmation with a saline suppression test should be done prior to any adrenal imaging or adrenal venous sampling. Spironolactone will interfere with confirmatory testing.

6. A 56-year-old man with monomorphic ventricular tachycardia is started on amiodarone. Baseline thyroid hormone levels were checked and were normal. Three months later, his TSH is 13.2 and free T4 is 0.6 ng/mL (normal range 0.8–1.8 ng/mL). What is the next step?
   A. Order radioactive iodine uptake scan
   B. Discontinue amiodarone therapy
   C. Start levothyroxine replacement therapy
   D. Obtain thyroid ultrasound
   E. Start methimazole therapy

   C—The patient has amiodarone-induced hypothyroidism, likely from a Wolff-Chaikoff effect from the iodine load from amiodarone treatment. The appropriate next step is to start levothyroxine replacement therapy at low doses and titrate up every 4–6 weeks until TSH is between 0.4 and 5 mIU/L. Thyroid ultrasound and RAI uptake scans are not useful in this situation as he is not hyperthyroid. Amiodarone has a long $t_{1/2}$ so even if it were to be discontinued, iodine-related effects will persist for many months. Methimazole is used to suppress thyroid hormone production in hyperthyroid states.

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CHAPTER 19

DOREEN DE FARIA YEH AND AMI B. BHATT

Adult Congenital Heart Disease (ACHD)

CHAPTER OUTLINE

ABBREVIATIONS

ACE	Angiotensin converting enzyme
ADHD	Adult Congenital Heart Disease
ALCAPA	Anomalous left coronary artery origin from the PA
AR	Aortic regurgitation
AS	Aortic stenosis
ASD	Atrial septal defect
AV	Atrioventricular
BAV	Bicuspid Aortic Valve
BP	Blood pressure
CC-TGA	Congenitally corrected Transposition of the Great Arteries
CHD	Congenital heart disease
CTA	CT angiography
CXR	Chest X Ray
EF	Ejection fraction
ICD	Implantable cardioverter defibrillator
LA	Left atrium
LAD	Left anterior descending
LBBB	Left bundle branch block
LV	Left ventricular

LVOT	Left ventricular out flow tract
MI	Myocardial infarction
MR	Mitral regurgitation
MV	Mitral valve
NO	Nitric oxide
PA	Pulmonary artery
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
PR	Pulmonic regurgitation
PS	Pulmonic stenosis
PVR	Pulmonary vascular resistance
RA	Right atrium
RBBB	Right bundle branch block
RCA	Right coronary artery
RV	Right ventricle
RVH	Right ventricular hypertertrophy
RVOT	Right ventricular outflow tract
SVC	Superior vena cava
SVT	Supraventricular tachycardia
TEE	Transesophageal echocardiogram
TGA	Transposition of the Great Arteries
TOF	Tetralogy of Fallot
TR	Tricuspid regurgitation
TV	Tricuspid valve
VSD	Ventricular septal defect
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White syndrome

LEFT-TO-RIGHT SHUNT LESIONS

Atrial Septal Defect (ASD)

- **Epidemiology**:
  - Most common congenital heart lesion in adults, female predominance
  - Rule out Holt Oram syndrome: autosomal dominant, congenital abnormality of the hand and radius, families should be screened
- **Types** (Fig. 19-1a):
  - Secundum (65%): varies in size, usually isolated lesion, mitral regurgitation (MR) occurs in elderly
  - Primum (10–15%): often large and associated with cleft anterior mitral leaflet with MR
  - Sinus venosus (10–15%): commonly associated with partial anomalous pulmonary venous drainage (superior sinus venosus defect—right upper pulmonary venous anomaly; inferior sinus venosus defect—right lower pulmonary venous anomaly: Scimitar)
  - Coronary sinus septal defects: rare, associated with complex cardiac lesions
- **Clinical Presentation**: ASD presents with a volume load to the right atrium (RA) and right ventricle (RV)
  - Varies from asymptomatic (incidentally found), to progressive RA and RV dilation with larger defects causing supraventricular tachyarrhythmia, fatigue, exercise intolerance.

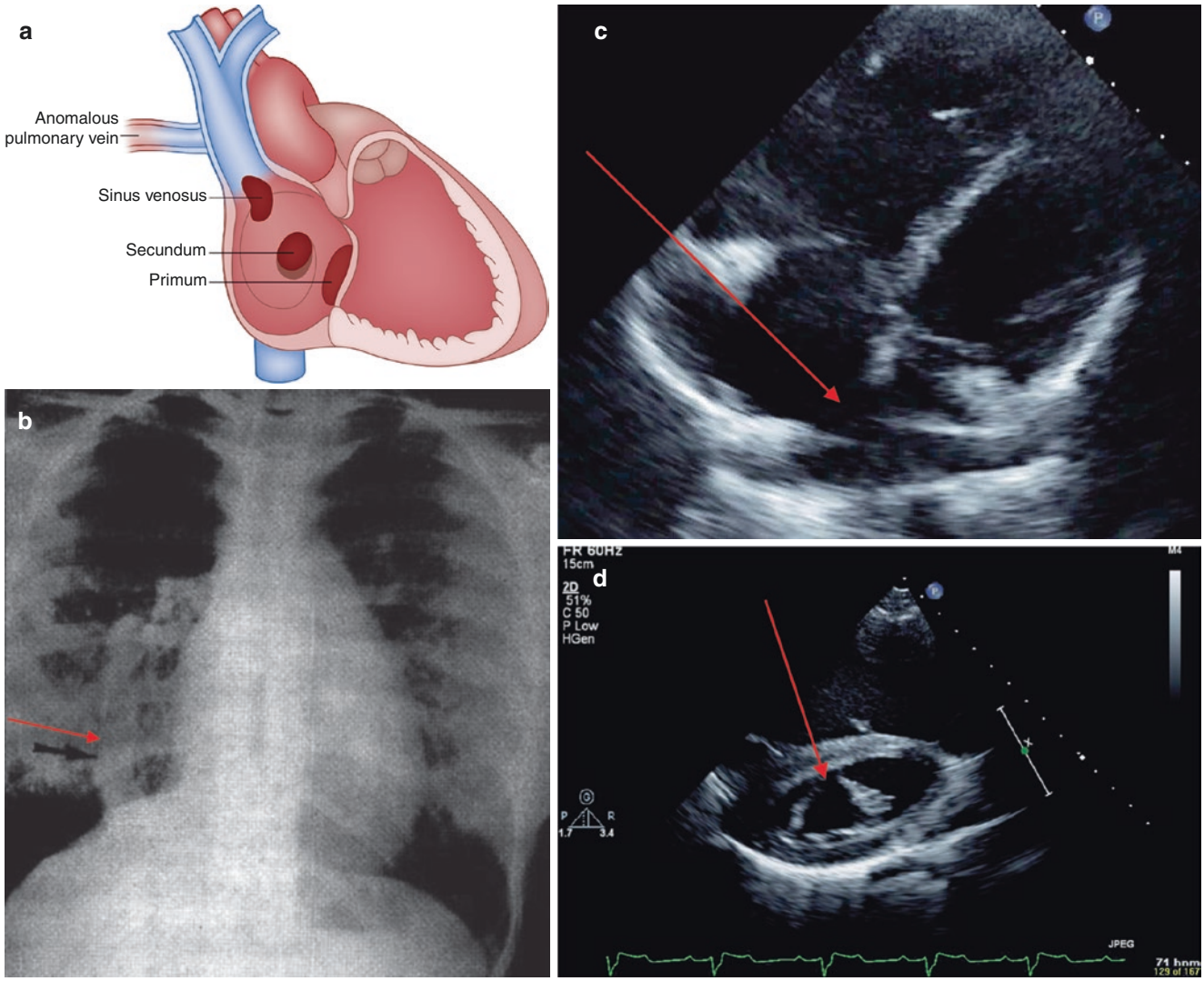


FIGURE 19-1

ASD. (**a**) Schematic of ASD location. (**b**) CXR of patient with Scimitar syndrome. Anomalous pulmonary venous drainage to the IVC (arrow) (**c**) Apical four chamber view with drop out of the interatrial septum consistent with large secundum ASD (arrow), note RV and RA enlargement. (**d**) Parasternal short axis view of a cleft mitral valve (arrow) often associated with primum ASD

- In older individuals (age >60): atrial fibrillation, and with a significant shunt, right heart dilation and hypocontractility. Left-to-right shunt may increase with advancing age as left ventricular (LV) compliance worsens, or systemic hypertension, MR, or LV disease develops
- Right ventricular hypertension may lead to right-to-left shunting, hypoxemia, cyanosis and rarely paradoxical embolus.
- Reversible flow-related pulmonary hypertension is common with large defects in older patients; irreversible pulmonary vascular obstruction is less common (Eisenmenger syndrome).

■ **Physical exam**:

- Wide and fixed splitting of the second heart sound
- Soft systolic pulmonary flow murmur
- Precordial lift (RV enlargement)

- **ECG findings**:
  - Incomplete right bundle branch block (RBBB), may progress to complete with larger shunts and age.
  - Primum defects typically have left axis deviation, sinus venosus and secundum generally have a rightward axis.
  - Sinus venosus may have a low ectopic atrial rhythm (negative p waves in leads II, III, aVF).
- **Chest X Ray (CXR)**: may reveal the curvilinear shadow of an anomalous pulmonary vein (with inferior sinus venosus defects, Scimitar sign Fig. 19-1b)
- **Echo findings**:
  - Right heart enlargement.
  - Atrial septal drop out (Fig. 19-1c).
  - Main pulmonary artery (PA) enlargement and increased transpulmonic flow.
  - In primum ASD, evaluation for mitral valve (MV) anterior leaflet cleft (Fig. 19-1d) and MR is important, rule out caval type ventricular septal defect (VSD).
  - In secundum ASD, a transesophageal echocardiogram (TEE) defines location and anatomy to determine candidacy for device closure.
  - Diagnosis of sinus venosus defect difficult with 2D echo and usually requires TEE.
- **CT/MR**: May be used for sinus venosus defect and partial vein imaging if not seen on echocardiogram.
- **Cardiac catheterization**: hemodynamic assessment of pulmonary vascular resistance (PVR) and reversibility (response to pulmonary vasodilator therapy: 100% O_2, nitric oxide [NO]), and shunt calculation is essential to determine closure candidacy. In some, test balloon occlusion in the catheterization lab may facilitate decision process.
- **Management**:
  - ACC/AHA Class I recommendations:
    - Pulse oximetry at rest and during exercise is recommended for evaluation of adults with unrepaired or repaired ASD with residual shunt to determine the direction and magnitude of the shunt [2].
    - CMR, CCT, and/or TEE are useful to evaluate pulmonary venous connections in adults with ASD
    - Echocardiographic imaging is recommended to guide percutaneous ASD closure
    - In adults with isolated secundum ASD causing impaired functional capacity, right atrial and/or RV enlargement, and net left-to-right shunt sufficiently large to cause physiological sequelae (e.g., pulmonary–systemic blood flow ratio [Qp:Qs] ≥1.5:1) without cyanosis at rest or during exercise, transcatheter or surgical closure to reduce RV volume and improve exercise tolerance is recommended, provided that systolic PA pressure is less than 50% of systolic systemic pressure and pulmonary vascular resistance is less than one third of the systemic vascular resistance
    - Adults with primum ASD, sinus venosus defect or coronary sinus defect causing impaired functional capacity, right atrial and/or RV enlargement and net left-to-right shunt sufficiently large to cause physiological sequelae (e.g., Qp:Qs ≥1.5:1) without cyanosis at rest or during exercise, should be surgically repaired unless precluded by comorbidities, provided that systolic PA pressure is less than 50% of systemic pressure and pulmonary vascular resistance is less than one third of the systemic vascular resistance
  - ACC/AHA Class III recommendation: ASD closure should not be performed in adults with PA systolic pressure greater than two thirds systemic, pulmonary vascular resistance greater than two thirds systemic, and/or a net right-to-left shunt [2].
  - Percutaneous closure: uncomplicated secundum defects with appropriate anatomy [3].
  - Surgical closure: large secundum ASDs, unusual anatomy, and all sinus venosus, primum ASDs and coronary sinus defects; Pre-operative imaging will define anomalous

pulmonary venous drainage and MV abnormalities that may also require repair. For sinus venosus defects with anomalous pulmonary venous drainage, a Warden technique is sometimes used.
- Post-operative complications: residual shunt, MR and atrioventricular (AV) conduction abnormality (rare, and all more likely with primum ASD repair). Sinus venosus surgical complications include sinus node dysfunction/supraventricular tachycardia (SVT), pulmonary venous obstruction at anastomosis site, and rarely superior vena cava (SVC) obstruction. Typically, RV size and function improve post operatively even in advanced age.

■ **Pregnancy and delivery**: well tolerated in most patients. Ideal to discuss and repair if needed preconception. With large bidirectional shunts, IV filters are recommended.

Ventricular Septal Defects (VSD)

■ **Epidemiology**: among most common congenital heart entities in early childhood, 2/3 close by early school age; larger VSDs present volume burden to the left atrium (LA) and LV and in some, the RV.

■ **Types** (Fig. 19-2a):

- Perimembranous: 60–70%
- Muscular: singular or multiple (10%), in adults generally small and restrictive
- Supracristal: (5%) more common in Asian populations, usually small defects located beneath the aortic annulus, may lead to progressive aortic leaflet prolapse and insufficiency (right and noncoronary cusp); typically asymptomatic until aortic regurgitation (AR) is severe.
- AV canal defect: common in Down's syndrome, typically involves anterior mitral cleft and occasionally cleft tricuspid septal leaflet; primum ASD may coexist

■ **Clinical presentation**: varies depending on prior management

- If small isolated restrictive defect, typically asymptomatic with a murmur
- If well repaired earlier, typically asymptomatic. Residual VSD is usually small, heart block may occur, and residual or recurrent AR (in a supracristal VSD) or MR (in AV canal VSD)
- If large defect uncorrected in childhood → Eisenmenger syndrome

■ **ECG**: typically RBBB (pre or post repair); marked left axis deviation (and sometimes AV block) with AV canal VSDs, right axis deviation/right ventricular hypertrophy (RVH) if significant pulmonary hypertension and in rare patients with progressive RV infundibular hypertrophy.

■ **Physical exam**:

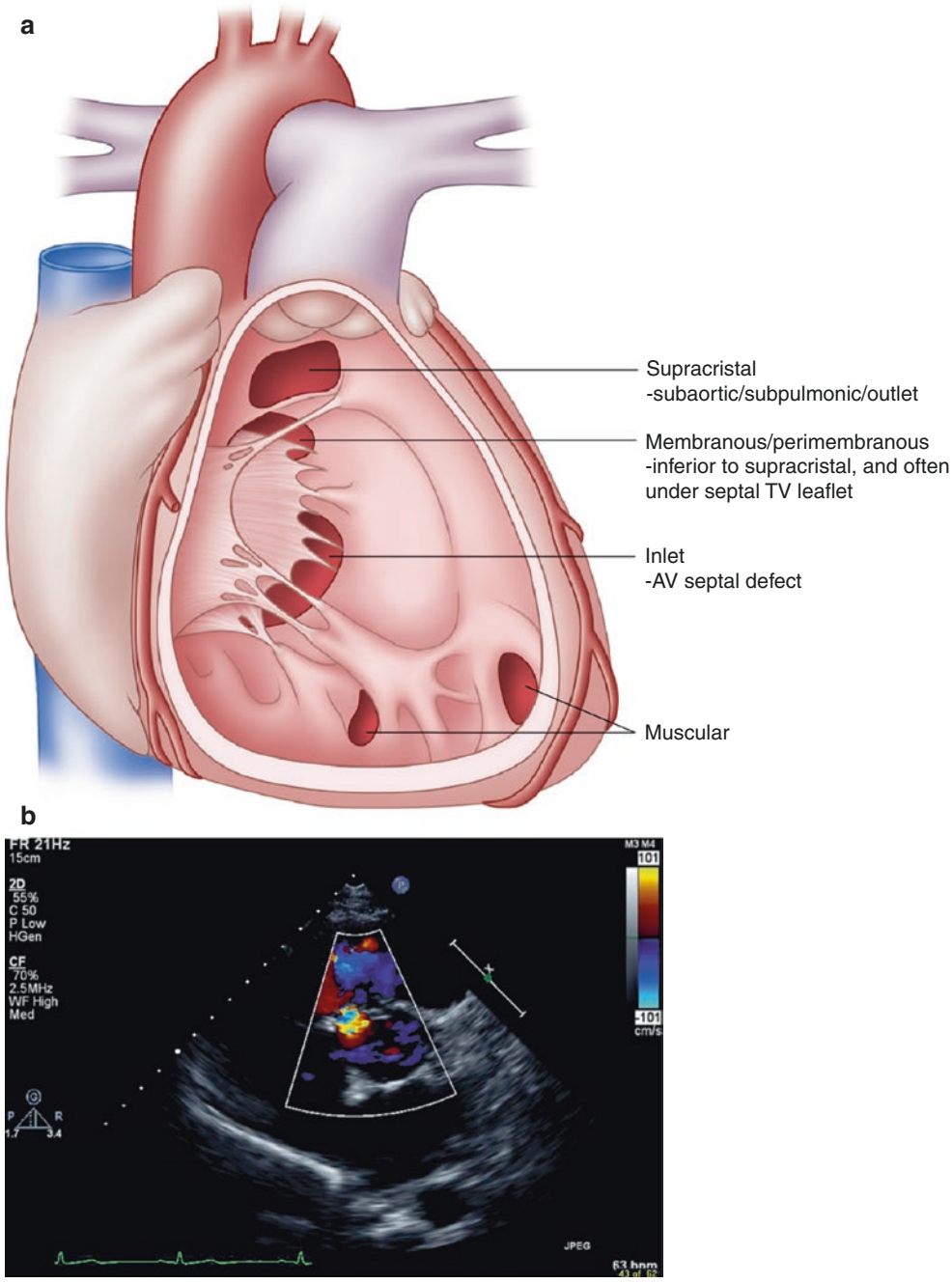
- Classic small restrictive VSD murmur is holosystolic, loud and harsh, augments with isometrics.
- Associated diastolic murmur of AR if aortic cusp prolapse is present
- In AV Canal patients, an MR or tricuspid regurgitation (TR) murmur from a cleft valve may also be appreciated
- If prior pulmonary banding (previously done in infancy to avoid pulmonary volume overload until corrective repair could be undertaken), a loud systolic ejection murmur of supravalvular pulmonic stenosis can be appreciated, and if RVH, there may be a jugular venous a wave on exam
- Eisenmenger exam-see below

■ **Echocardiography**:

- Define detailed VSD anatomy (Fig. 19-2b), estimate RV pressure and gradient across the defect(s), and identify associated lesions
- If corrected, evaluate for residual shunt and assess RV pressure and rule out associated lesions

FIGURE 19-2

VSD. Ventricular septal defects. (**a**) Schematic of VSD location. (**b**) Echo image (parasternal short axis view) of perimembraneous VSD, systolic flow noted around 10′o clock



- **Catheterization**: performed pre-operatively for pulmonary vascular assessment, coronary screening in older patients, and de fi ne associated lesions.
- **Management**:
  - Small, restrictive lesions rarely require specific management
  - ACC/AHA Class I recommendation: Adults with a VSD and evidence of left ventricular volume overload and hemodynamically significant shunts (Qp:Qs ≥1.5:1) should undergo VSD closure, if PA systolic pressure is less than 50% systemic and pulmonary vascular resistance is less than one third systemic [2]
  - ACC/AHA Class III recommendation: closure of a VSD is not recommended in patients with severe irreversible pulmonary hypertension [2]
  - Role for percutaneous approach is evolving for VSDs remote from the tricuspid valve (TV) and aorta

- **Complications**:
  - Endocarditis
  - Potential right-to-left thrombotic complication avoid intracardiac RV pacer or implantable cardioverter defibrillator (ICD) wires
  - Progressive aortic cusp prolapse and insufficiency, and rarely sinus of Valsalva aneurysm or fistula (fistula will result in continuous murmur)
  - Large VSDs left untreated may lead to increased PVR from long term increased pulmonary flow, and reversal of the shunt (Eisenmenger syndrome).
  - Heart block is an occasional early or late post-operative complication

Patent Ductus Arteriosus (PDA)

- **General**: PDA is essential for prenatal survival. It typically closes early in infancy, with a higher incidence of PDA in premature infants and those living at high altitudes. Commonly associated with Congenital Rubella Syndrome as is branch pulmonic stenosis.
- **Clinical Presentation**: varies according to size, from asymptomatic (incidentally noted), to LA and LV volume overload or Eisenmenger syndrome when large and unrepaired
- **Physical Exam**:
  - Small PDA: soft continuous infraclavicular, left sternal border or left upper back murmur, enhanced with isometrics (Fig. 19-3)
  - Moderate PDA: ventricular enlargement and a displaced point of maximal impulse on palpation
  - Large PDA: LA and LV enlargement; If pulmonary hypertension, there will be a prominent pulmonic component to the second heart sound and RV heave with cyanosis and clubbing [Eisenmenger individual: may have differential cyanosis: cyanosis of feet (clubbing of toes) and perhaps left hand with normal right hand pulse oximetry]
  - Differential for continuous murmur includes: PDA, coronary AV fistula, aortopulmonary window, pulmonary AV malformation (Peutz Jaeger syndrome) or the systolic/diastolic murmur of aortic stenosis (AS)/AR
- **Complications**: endarteritis, left heart failure, pulmonary vascular disease if large and unrepaired; in older adults calcification, aneurysm and dissection risk which may complicate repair
- **Management**:
  - ACC/AHA Class I recommendation: PDA closure in adults is recommended if left atrial or LV enlargement is present and attributable to PDA with net left-to-right shunt, PA systolic pressure less than 50% systemic and pulmonary vascular resistance less than one third systemic [2]
  - ACC/AHA Class III recommendations: closure is not indicated if pulmonary hypertension with net right-to-left shunt [2]

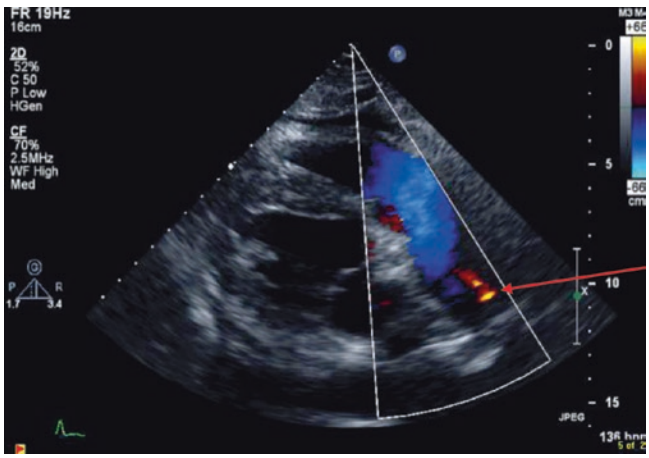


FIGURE 19-3

PDA. Patent ductus arteriosus: modified parasternal view with laminar flow across the pulmonic valve leaflets and main PA, and PDA flow from the aorta into the LPA (arrow)

Sinus of Valsalva Fistula

- **Description**: Typically arise from the right or noncoronary sinus of Valsalva and enter the right heart. May be associated with a VSD high in the basal septum; Commonly associated with connective tissue abnormality
- **Clinical presentation**: new onset prominent diastolic or continuous murmur, occasionally precipitated by strenuous isometric exertion
- **Management**:
  - Endocarditis and AR risks exist
  - Surgical repair; transcatheter occlusion for selected patients
  - Recurrence may occur

OBSTRUCTIVE LESIONS

Left Ventricular Out Flow Tract (LVOT) Obstruction

Congenital Aortic Valvular Stenosis

- **Bicuspid Aortic Valve (BAV):**
  - **Epidemiology**: most common congenital heart lesion, male predominance, estimated 1–2% of population, may be familial, multiple morphologic variants, may be undiagnosed for many years
    - Can be associated with aortic coarctation, should be ruled out in Turner's Syndrome
    - Important association with medial connective tissue abnormalities of the ascending aorta
      - Abnormalities of smooth muscle, extracellular matrix, elastin and collagen of the ascending aorta sometimes result in progressive dilation and increase dissection risk with age
      - Ascending aortic dilation does not correlate with valve stenosis severity
  - **Clinical presentation and physical exam**: varies with severity of stenosis or regurgitation
    - Asymptomatic evident by only soft systolic flow murmur and early systolic ejection sound (uncommon after age 40 years)
    - Severe LV out flow obstruction, syncope, chest pain, heart failure and endocarditis
    - Stenosis may be progressive in mid-life as well as with advanced age and renal dysfunction
    - Regurgitation is less common than stenosis
  - **Echocardiography**:
    - Mean Doppler gradients correlate well with transcatheter pull back gradients
    - Important to assess ascending aortic dimensions serially (frequency of imaging varies with size of aorta at initial assessment: if <40 mm → every 2 years, if ≥40 mm → annually or more frequently if rapid change or new symptoms) even in previously operated aortic valve patients who have not had prior ascending aortic intervention. CT angiography (CTA) is preferable as aortic size approaches surgical dimensions (see below).
  - **Intervention**: transcatheter balloon dilation may be appropriate in younger adults with severe stenosis without significant AR, otherwise, surgical valvuloplasty or valve replacement per valve guidelines.
    - ACC/AHA Class I recommendation: aortic surgical intervention is indicated in a patient with a BAV and ascending aorta is 5.0 cm or more, or if there is progressive dilatation at a rate greater than 5 mm per year [2]

- **Unicuspid aortic valve**: rare, may present with stenosis or regurgitation. It may be associated with ascending aortic dilation. Transcatheter balloon dilation may cause AR, therefore surgical intervention for severe obstruction or insufficiency is recommended.
- **Quadricuspid aortic valve**: very rare. Presents typically late in life with AR requiring aortic valve replacement, stenosis is rare.

Discrete Subaortic Membrane

- **General**:
  - Congenital or acquired, (occasionally associated with primum ASD, double chamber RV, or tetralogy of Fallot [TOF])
  - Prevalence among patients with ACHD is approximately 6.5%.
  - Membranes vary in thickness, morphology and distance below the aortic valve (Fig. 19-4), AR is common due to high velocity flow jet causing aortic valve sclerosis
  - Familial occurrence approaches 15% among primary relatives (who should be screened)
  - Bacterial endocarditis occurs
  - Infrequent ascending aortic dilation
- **Physical exam**:
  - Systolic crescendo decrescendo murmur and absence of ejection sound
  - AR murmur (more than 50%)

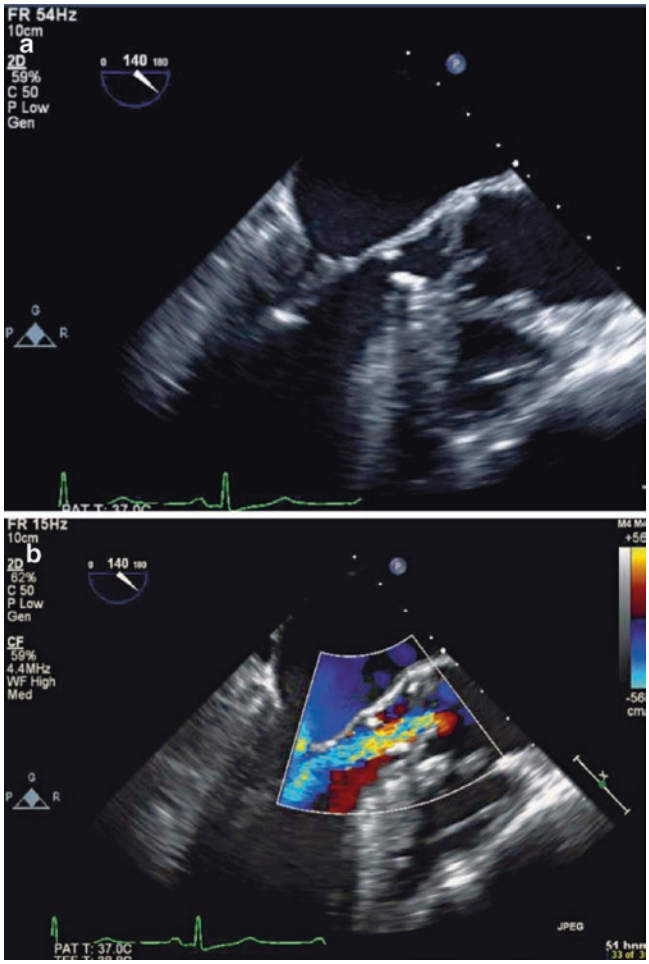


FIGURE 19-4 (**a**) TEE, subaortic membrane noted approximately 1.2 cm below the aortic valve along the anterior surface of the ventricular septum, as well as the anterior aspect of the mitral valve. Note the aortic valve leaflets appears thickened and degenerated. (**b**) Associated aortic insufficiency. Courtesy: Yale University School of Medicine, Congenital Heart Disease website

■ **Management**:

- Percutaneous balloon dilation is rarely successful
- Surgical resection for significant obstruction or insufficiency, aortic valve should be evaluated at the time of surgery as well.
  - ■ ACC/AHA Class I recommendations:
    - Surgical intervention is recommended for adults with a maximum gradient 50 mmHg or more and symptoms [2]—however each case should be considered independently as significant heterogeneity exists.

■ **Post operative issues**:

- Residual hypertrophic LVOT obstruction, AR, left bundle branch block (LBBB) or surgical VSD can occur
- Membranes may recur post operatively (15%)

Supravalvular Aortic Stenosis

Ascending aortic narrowing (Fig. 19-5) commonly associated with Williams Syndrome. Obstruction may be discrete or diffuse, may extend variably cephalad in the ascending aorta and arch. Generally, spares the coronary arteries and aortic valve. Surgical revision when obstruction is significant. Differential diagnosis includes:

Takayasu and rarely homozygous hypercholesterolemia with secondary lipomatous deposition in the proximal ascending aorta.

Coarctation of the Aorta

■ **Definition/anatomy**:

- Typically focal narrowing in the region of the ligamentum arteriosum adjacent to the origin of the left subclavian artery (Fig. 19-6a)
- May be discrete obstruction or more diffuse narrowing extending proximally towards the arch, may involve associated stenosis of the left subclavian artery
- Distal origin of the right subclavian below the coarctation site occurs in a small percentage and masks the hypertension seen by the coronary arteries and cerebral vasculature as both arm blood pressures may be reflective of post-coarctation pressure.
- Presence of large collaterals may reduce the gradient across the coarctation site
- Shone's complex: coarctation associated with left heart obstructions (subaortic stenosis, BAV, parachute MV, or supramitral ring)

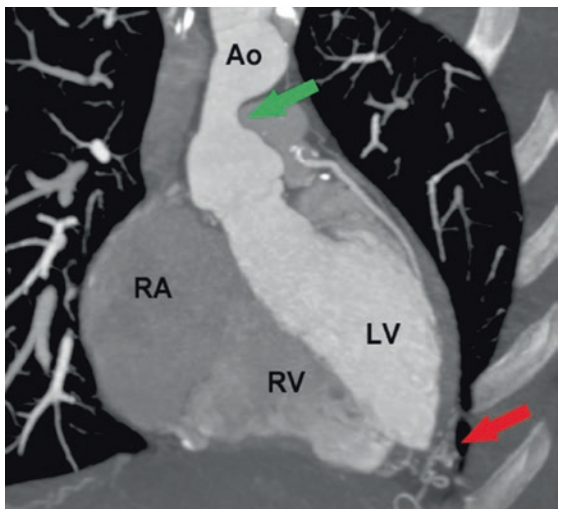


FIGURE 19-5

Supraaortic stenosis. William syndrome, supraaortic stenosis (green arrow) Red arrow depicts collateral vessels CTA. (Courtesy of Sidhu MS et al. MGH cardiovascular imaging)

- **General**:
  - Male predominance
  - Associated with BAV (50–60%)
  - Associated circle of Willis aneurysm (ACC/AHA Class I recommendation: Intracranial vessels should be screened with MR or CT in all patients with coarctation [2])
- **Physical exam**:
  - Pulse and blood pressure evaluation in all four extremities
  - BAV findings (when present): systolic ejection sound, precordial out flow murmur, AR Murmur
  - Coarctation findings:
    - Systolic bruit over the upper left back
    - Radial-femoral delay
- **CXR findings**:
  - Aortic indentation at the coarctation site "3 sign" (Fig. 19-6b)
  - Notching on the underside of the ribs from collateral vessels
- **Echocardiography**:
  - Best viewed from suprasternal notch
  - May see collateral vessel flow (also well defined by MRI and CTA Fig. 19-6c)
  - Abdominal aorta demonstrates anterograde diastolic flow (Fig. 19-6d)
- **Indications for surgical or percutaneous intervention**:
  - ACC/AHA Class I recommendation: Initial and follow up imaging with MRI or CTA is indicated in adults with CoA, resting BP should be measured in all extremities, (Fig. 19-6e) Surgical repair or catheter-based stenting is recommended for adults with hypertension and significant native or recurrent coarctation of the aorta [2]
  - Percutaneous approach may be considered in experienced hands if narrowed site is amenable
  - Surgical intervention for complex anatomy, long segment tubular lesions, prior aneurysm, calcification or poorly compliant arterial system.
  - Advanced imaging, whether MRI or CT, may add to delineation and management
- **Long term follow up**:
  - Lifelong adult congenital cardiology follow up is advised with interval assessment for development of resting or exercise-induced hypertension
  - Repair or re-repair is appropriate regardless of advanced age
  - For complex coarctation, bypass grafting from left subclavian artery to descending aorta or ascending to descending aorta is often advisable.
  - ACC/AHA Class I recommendation: evaluation of coarctation repair site by MRI/CT should be performed at intervals of 5 years or less (depending on anatomy of repair) to assess for coarctation site aneurysm or residual obstruction [2]
- **Pregnancy**:
  - With unrepaired or postoperative recurrent coarctation, as well as with aneurysms, there is an increased risk of 3rd trimester or peripartum dissection, which may be fatal
  - Hypertension and pre-eclampsia may also occur in select individuals
  - Pre-pregnancy counseling is critical, maternal and fetal risks can exist and vary based on prior repair and anatomy
  - Pre-pregnancy coarctation imaging is essential to inform risk discussion
  - Genetic transmission should be discussed and fetal echocardiography is recommended

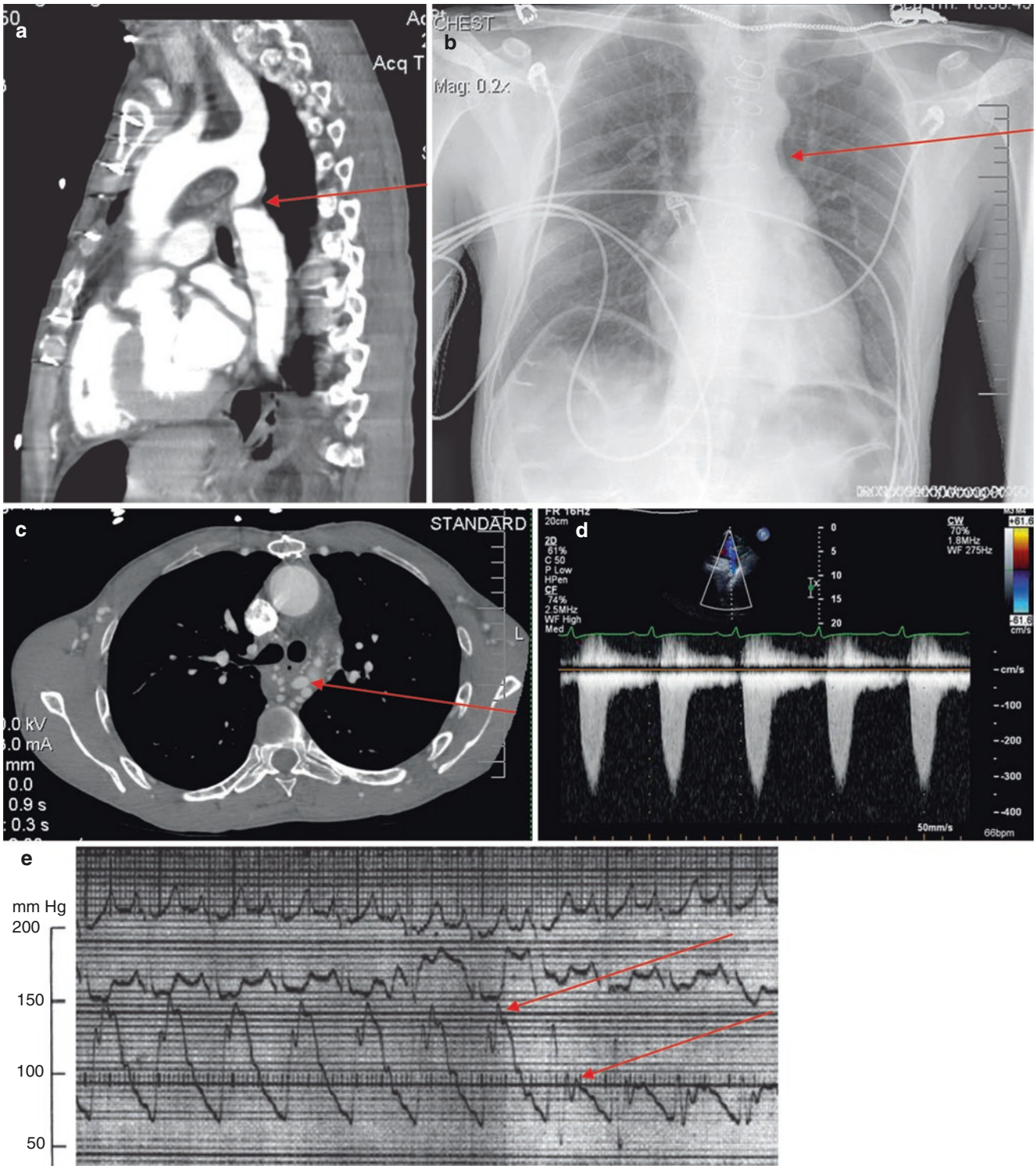


FIGURE 19-6

Aortic coarctation. (**a**) Sagital imaging, CT angiography with discrete aortic coarctation (arrow). (**b**) CXR with 3 sign (arrow), note subtle rib notching. (**c**) Axial imaging, CT angiography with small proximal descending aorta, and multiple collateral vessels. (**d**) Abdominal aortic pulse wave Doppler in aortic coarctation showing significant anterograde diastolic flow, consistent with severe obstruction. (**e**) Coronary angiography with catheter pullback across the coarctation demonstrating significant drop in pressure distal to the coarctation site

Right Ventricular Outflow Tract (RVOT) Obstruction

Pulmonic Stenosis (PS)

- **Valvular PS**: Congenital PS most often occurs at valve level, whether bi or tricommissural.
  Varies significantly in severity and clinical presentation.
  - Noonan syndrome may be associated with myxomatous valvular PS (may also have associated LV hypertrophic cardiomyopathy)
- **Physical exam**:
  - Systolic ejection murmur (intensity, time to peak and duration, vary with severity)
  - Presence of early systolic ejection sound; closer the ejection sound to S1, the more severe stenosis—of note the pulmonic valve ejection click is the only right heart finding which decreases in intensity with inspiration
  - Pulmonic closure intensity decreases and delay of P2 from A2 increases with severity of stenosis.
  - Jugular venous a waves and RVH are present in significant stenosis
  - Low pitched diastolic murmur of PR may coexist
    - **Echocardiography**: defines and quantifies PS anatomy and severity
- **CXR**:
  - Prominent main and left pulmonary branch dilation (even if stenosis is not severe)
- **Management**:
  - Surgically managed since the mid 1950s with excellent survival
  - Since early 1980s, transcatheter balloon dilation has supplanted surgery for a majority
  - Balloon valvotomy—ACC/AHA Class I recommendations [2]:
    - In adults with moderate or severe valvular pulmonary stenosis and otherwise unexplained symptoms of HF, cyanosis from interatrial right-to-left communication, and/or exercise intolerance, balloon valvuloplasty is recommended
    - Moderate or greater PR is a relative contraindication.
- **Supravalvular PS**: (or Branch PS) is uncommon but noteworthy and occurs in Congenital Rubella syndrome, Williams syndrome and Takayasu arteritis. Balloon dilation is favored if the lesion in amenable. May occur iatrogenically in the branches from previous systemic to pulmonary palliative shunts, or at the main PA from prior pulmonary artery banding.
- **Subpulmonic stenosis**: rare but does occur in patients with valvular PS, tetralogy of Fallot and some transposition patients.
- **Double chambered RV**: Anomalous muscle bundles that divide the RV into a higher pressure proximal chamber and a lower pressure distal chamber. Associated lesions are VSD, valvular PS, subaortic membranes. In the elderly, double chambered RV may be complicated by ventricular tachyarrhythmia.

Tetralogy of Fallot (TOF)

- **General**:
  - Most common cyanotic congenital heart lesion after infancy
  - Spectrum of morphology and severity, with pulmonary atresia and VSD the most severe form
- **Anatomy**: RV outflow obstruction (valvular and subvalvular/infundibular with generally small pulmonary arteries), large VSD with an overriding aorta and RV hypertrophy (Fig. 19-7a). Right aortic arch is associated in 25% of cases. Suspect TOF as a diagnosis in cyanotic patients with a right aortic arch.

- ~5% of TOF patients have aberrant course of the left anterior descending (LAD) or left main arising from the proximal right coronary artery (RCA) or right sinus of Valsalva, traversing the RVOT (coronary anatomy should be assessed preoperatively)
- Approximately 15% patients have ascending aortic dilation, most notably those with AR, right aortic arch, and severe degrees of pulmonary stenosis, particularly pulmonary Atresia

■ **Clinical presentation in adults**:

- Patients present s/p remote palliative procedures (see below), but most present s/p remote complete repair. It is rare to present as an adult with no prior interventions, though teenagers in immigrant populations may present with native disease.
- Post complete repair: asymptomatic or may have significant late complications including significant pulmonary insufficiency and RV dilation and dysfunction, and ventricular tachycardia (VT), sudden cardiac death.

■ **Physical exam**:

- Evidence of residual RVOT obstruction with systolic murmur over the pulmonic area
- Harsh holosystolic murmur of a residual VSD
- Pulmonary incompetence: low-pitched diastolic decrescendo murmur; shorter murmurs generally more severe

■ **ECG**:

- RBBB, RVH, RA enlargement (Fig. 19-7b)
- T wave inversions over anterior precordium
- PR prolongation and complete heart block rarely
- SVT or VT

■ **Palliative interventions** (Fig. 19-7c and Table 19-1): do not correct the pulmonary stenosis or the right-to-left shunt

- Blalock-Taussig shunt is most common. Waterston and Potts are rarely used today.
- Blalock-Taussig shunt (subclavian artery to branch PA): allowed survival to complete repair; ligated at time of complete repair
- Potts shunt (descending aorta to left PA window): may be complicated by pulmonary vascular obstruction of the left lung or left PA hypoplasia (challenging surgical revision)
- Waterston shunt (ascending aorta to right PA window): complications include right PA stenosis and hypoplasia. Transcatheter right PA dilation may be helpful

■ Rastelli procedure: (See Table 19-1, Fig. 19-18) used in patients who have degrees of transposition of the great arteries associated with their VSD and pulmonary stenosis where traditional complete TOF repair is not possible

- Baffle from the LV to the ascending aorta (occasionally complicated by AV block) and valved conduit placement from the RV to the main PA
- Late stenosis of the RV to PA conduit is common and requires with either percutaneous dilation or surgical replacement. Experience with percutaneous valve placement in the Rastelli conduit is growing at select institutions.
- Stenosis occurs at the take-off or touch down conduit site or at the level of the valve within the conduit (transcatheter techniques for pulmonary valve dilation or replacement are rapidly evolving)

■ **Complete repair** (VSD closure, RVOT augmentation): now mostly performed in infancy or early childhood

■ **Late post repair complications**:

- PR may be progressive over several decades (Fig. 19-7d). ACC/AHA Class I recommendation: Pulmonic valve replacement is indicated for severe PR with any of the following: (1) symptoms of decreased exercise tolerance, (2) moderate to severe RV

dysfunction or enlargement (3) sustained atrial or ventricular arrhythmias or (4) moderate to severe TR [2]
- Significant residual VSD is increasingly less common as is significant residual PS.
- SVT is increasingly common beyond the fifth decade
- Ventricular tachycardia (VT)/fibrillation (sudden cardiac death):

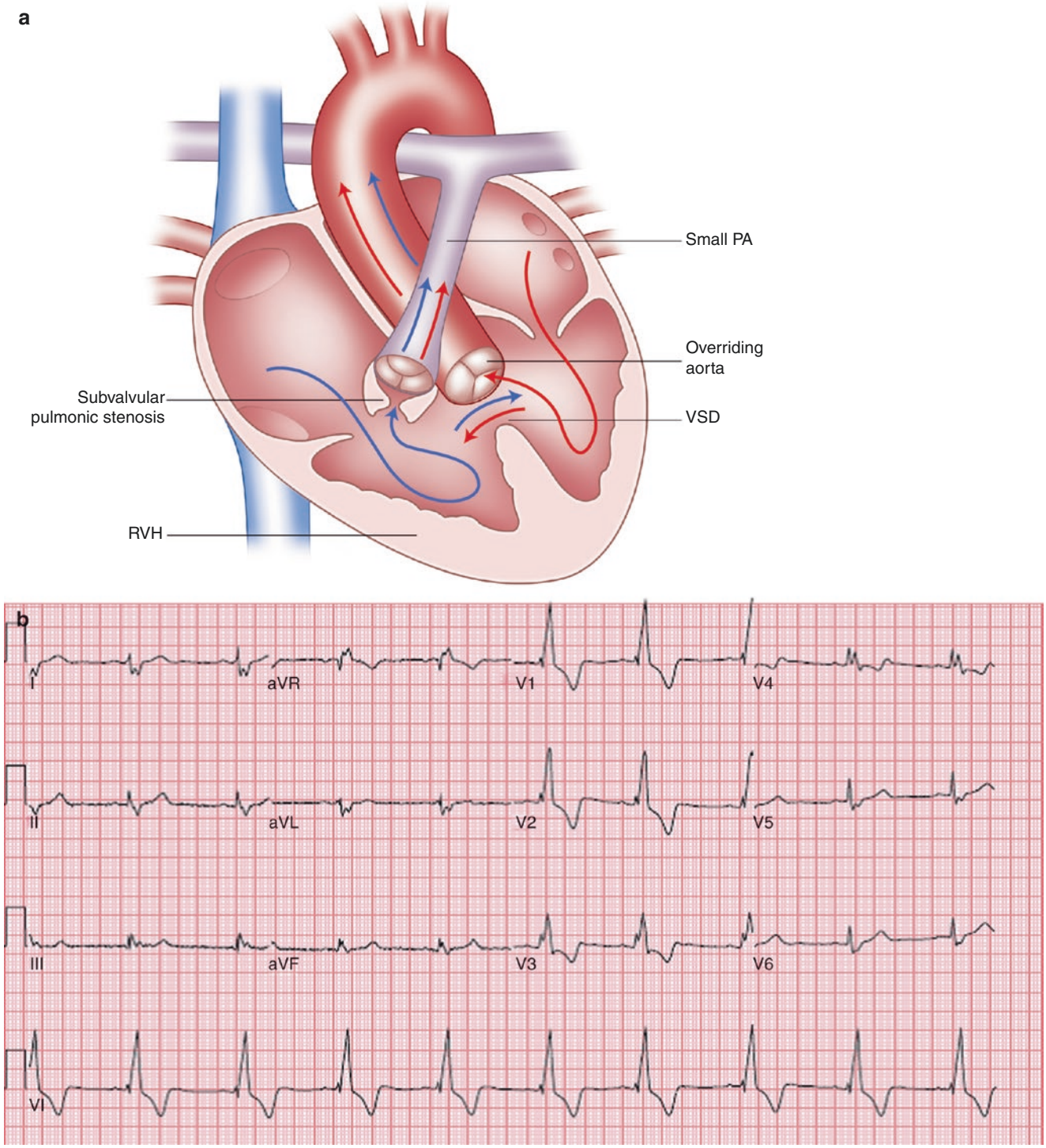
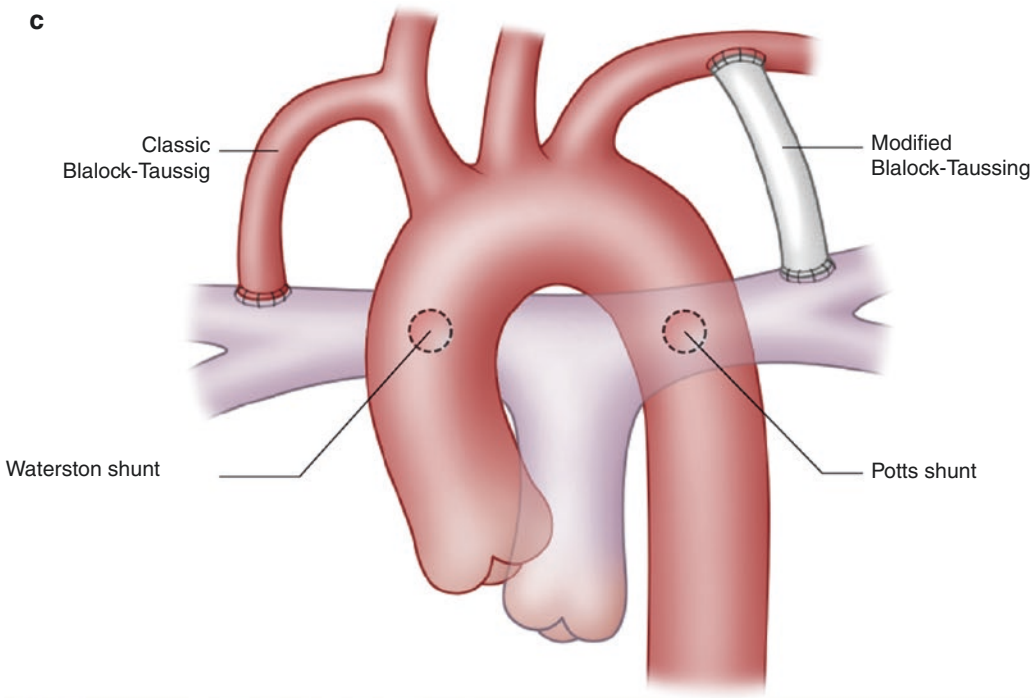


FIGURE 19-7

TOF. Tetrology of Fallot. (**a**) Schematic of TOF anatomy. (**b**) ECG with right bundle branch block, RVH, precordial TWI (patient with TOF status post repair with severe PR and RV dilation). (**c**) Palliative interventions in TOF. (**d**) Echo of severe PR: continuous wave Doppler across the RVOT, note steep deceleration of pulmonic regurgitant jet. Correlates with short decrescendo diastolic murmur



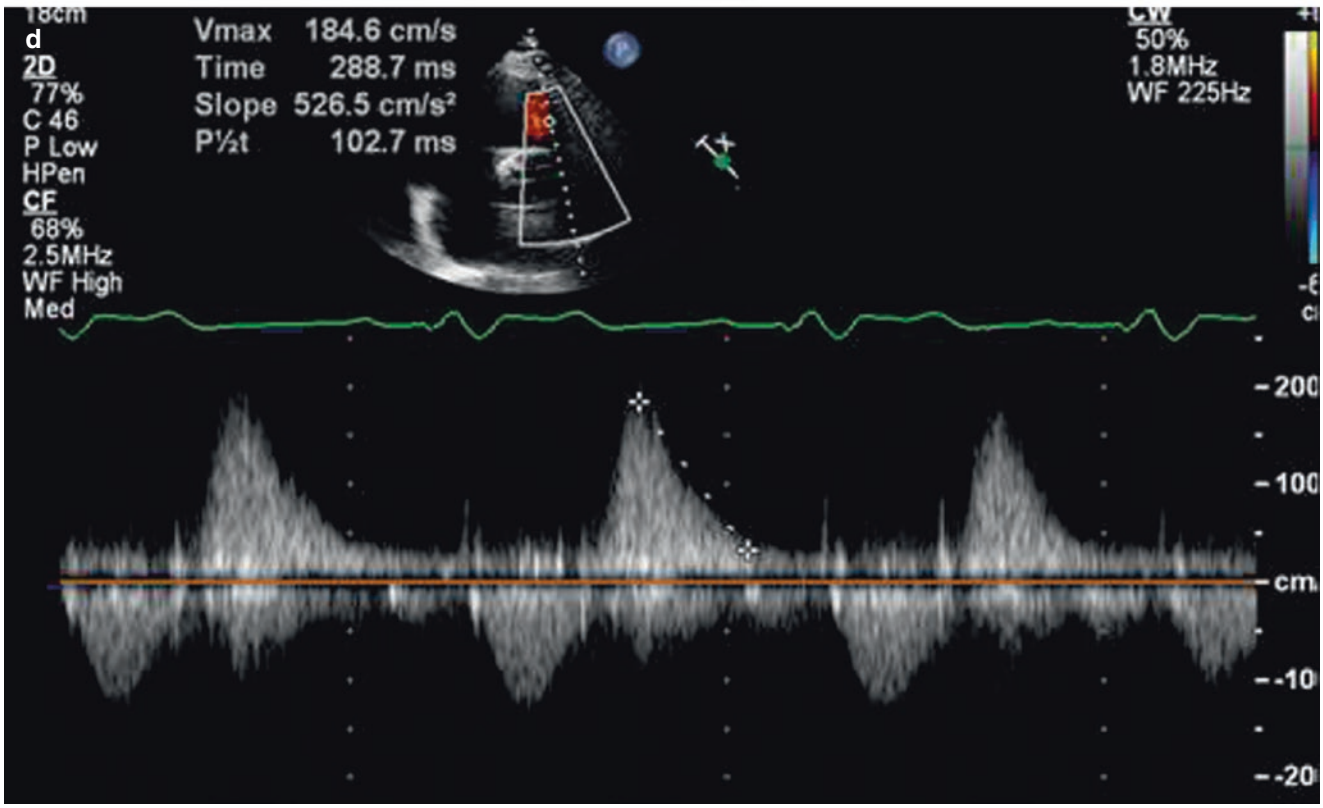


FIGURE 19-7

(continued)

TABLE 19-1

SURGICAL PALLIATION OR CORRECTIVE PROCEDURES

SURGICAL PALLIATION OR CORRECTION	DESCRIPTION	COMPLICATIONS
Blalock Taussig Shunt (Fig. 19-7c)	Subclavian artery to branch PA connection	Reduced BP and pulse in affected arm
Waterston Shunt (Fig. 19-7c)	Ascending aorta to PA shunt	Pulmonary overcirculation if left open for too long
Potts Shunt (Fig. 19-7c)	Descending aorta to PA shunt	Pulmonary overcirculation, left PA kinking and difficulty ligating due to challenge of approaching from a sternotomy
Mustard/ Senning (Fig. 19-9b)	Atrial switch for D TGA- redirects venous inflow (Mustard: pericardial or Gore-Tex patch, Senning: native atrial tissue)	Atrial arrhythmias, baffle obstruction, baffle leak, systemic right ventricle failure, systemic TR, ventricular arrhythmias
Jatene Arterial Switch (Fig. 19-9e)	Arterial switch for D TGA (began in 1980s)	Aortic dilation, coronary reimplantation concerns, suprapulmonic or supraaortic anastomotic site stenosis
Glenn Shunt	SVC to right PA shunt	Right pulmonary AVMs if no IVC flow is presented to right lung
Fontan (total cavopulmonary anastomosis) (Fig. 19-11)	Redirecting systemic venous return to the lungs without a ventricular pump (RA to PA, Lateral tunnel, Extracardiac)	Atrial arrhythmias, baffle leak (cyanosis), RA thrombus, thromboembolism (deep venous thrombosis, pulmonary embolus, stroke), liver dysfunction/ascites, systemic to pulmonary venous collaterals (causing cyanosis), ventricular dysfunction, Failing Fontan (protein losing enteropathy, plastic bronchitis)
Rastelli (Right ventricle to PA conduit) (Fig. 19-18)	Used in Double outlet right ventricle and D-TGA morphology most commonly. LV to aortic flow is usually via a VSD	RV to PA conduit stenosis and insufficiency (may require multiple reinterventions). RVH. Right heart failure symptoms
PA Banding	Surgically created stenosis of the main PA; palliative procedure to protect the lungs against high pulmonary blood flow when definitive repair is not immediately feasible	Band site PA stenosis; RV hypertension
Warden procedure	intracaval baffle technique in SV ASD with PAPVD in the SVC	Bradycardia and junctional rhythm, SVC obstruction

- High risk features: LV dysfunction, palliation for many years prior to complete repair/older age at time of repair, significant RV dilation and dysfunction, high RV mass to volume ratio, inducible VT on electrophysiology testing, and QRS duration >180 ms
- Aggressive antiarrhythmic management and assessment and implantable defibrillator should be considered in high risk patients. It is important to address repair of significant hemodynamic lesions in patients with an arrhythmia burden as well.

- **Pregnancy**:
  - Well repaired stable TOF adults manage well through pregnancy and delivery, but always advisable to involve high risk obstetrics and congenital heart specialist
  - Risk of right heart failure and arrhythmia is increased with significant RV dysfunction

Ebstein Anomaly

- **General**: approximately 1% of all CHD, wide spectrum of severity of anatomic and functional abnormalities of the TV and RV
- **Anatomy**: "Apical displacement" of the TV caused by failure of delamination of the tricuspid leaflets from the RV muscle, compromise in size of the portion of the RV below the TV and enlargement of the RA by portion of the RV above the TV ('atrialized' RV)
- **Major clinical issues**:
  - Degree of tricuspid regurgitation
  - RV cardiomyopathy/RV function
  - Presence of an associated interatrial communication (ASD or stretched patent foramen ovale [PFO])
  - Atrial arrhythmias
- **Clinical presentation is highly variable**:
  - From asymptomatic with a nearly silent clinical exam to marked right heart failure, cyanosis, and early death
  - Wolff-Parkinson-White syndrome (WPW) is present in 25% of patients and presents with palpitations or SVT. Ventricular arrhythmias may occur.
  - Progressive exercise intolerance and fatigue from TR and RV dysfunction may occur
  - Acute systemic desaturation from right-to-left shunt through an ASD or PFO is poorly tolerated. Paradoxical embolus can rarely occur.
- **Clinical exam**
  - Tricuspid holosystolic murmur and multiple systolic clicks exist but can be subtle
  - Both first and second heart sounds are widely split
  - "Sail sound" of a loud systolic sound created by the large anterior leaflet may be heard
  - Rocking motion of the heart with an easily palpable RV in more severe disease
  - Right heart failure: elevated jugular venous pressure, hepatojugular reflux, lower extremity edema, hepatic congestion, cyanosis
- **ECG**: wide and splintered QRS complex (right precordial leads), RA enlargement, first degree AV block and when present, Type B WPW pattern (Fig. 19-8a)
- **CXR**: varies with severity and shows RA enlargement, pulmonary vasculature usually normal unless marked cyanosis, and cardiac silhouette can be massive with enlargement progressing with age (Fig. 19-8b).
- **Echocardiography** is the diagnostic gold standard and defines anatomy and severity of TR, RV size and function, RA size, interatrial communication and associated LV abnormalities (Fig. 19-8c).
- **Management**:
  - IV filters when ASD or PFO present
  - SVT and accessory pathway management can be challenging secondary to multiple bypass tracts, variation in atrialized RV and tricuspid annular anatomy, thickened atrialized RA tissue and thin RV walls.
  - Anticoagulation is recommended if history of paradoxical embolism or atrial fibrillation
- **Surgical timing**: cannot be generalized and differs with each individual
  - Surgery is best performed in experienced centers
  - Options include TV repair vs. replacement, inter-atrial communication closure, simultaneous Maze procedure, and in some, cardiac transplant
  - Post operatively: management includes avoidance of right ventricular afterload and positive pressure, and arrhythmia and AV block surveillance.
- **Pregnancy**: pre-pregnancy counseling is important; successful delivery is often accomplished without difficulty in uncomplicated patients; but with significant RV failure, TR, and cyanosis, pregnancy should be discouraged.

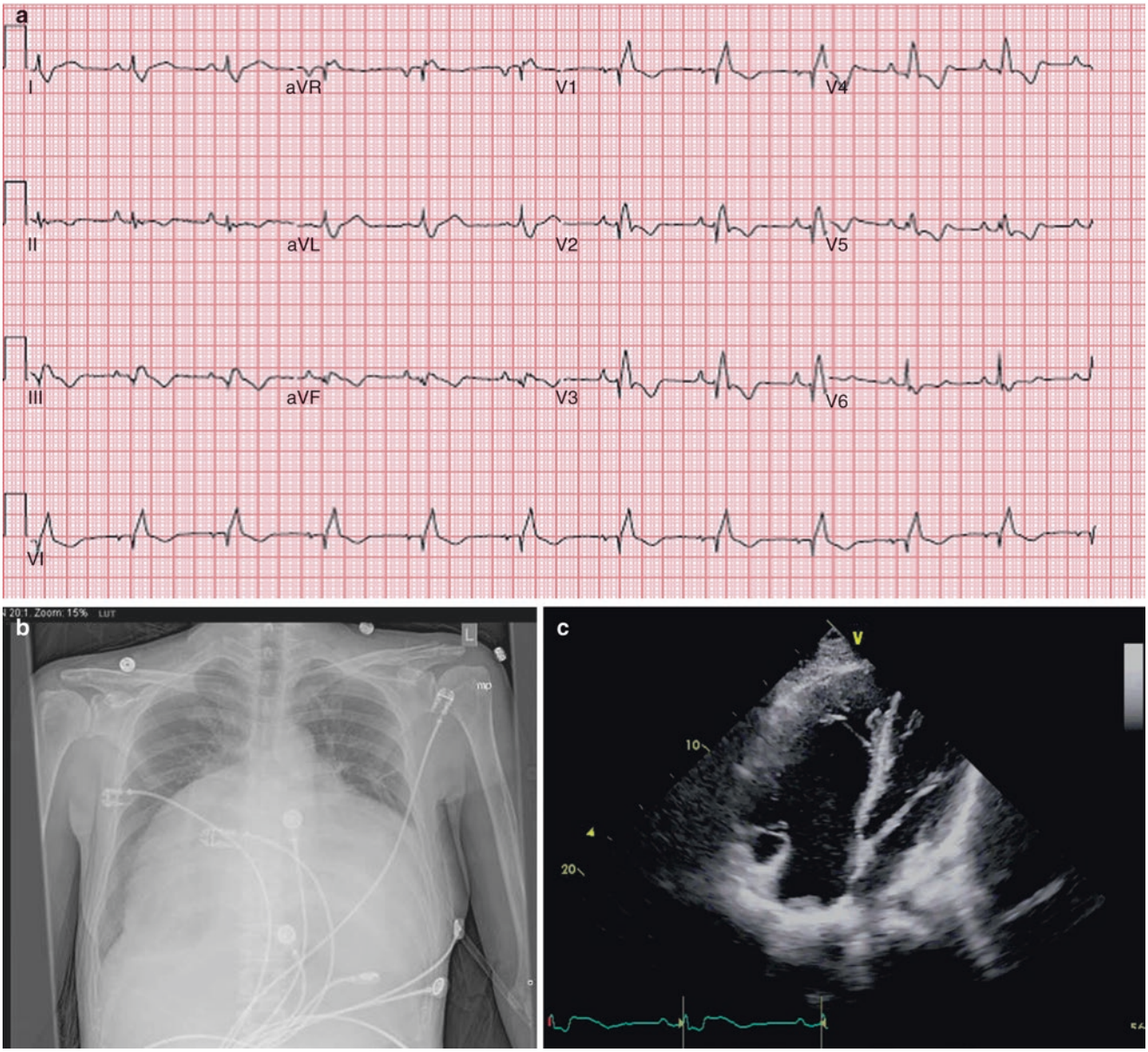


FIGURE 19-8

Ebstein's anomaly. (**a**) ECG showing right axis deviation, first degree AV block and complete right bundle branch block with marked splintering of the R′ deflection. (**b**) CXR of Ebstein demonstrating severely enlarged heart. (**c**) Four chamber echo image with apical displacement of the septal tricuspid leaflet and RV enlargement

Transposition of the Great Arteries (TGA)

■ **D-TGA**:

- **Anatomy**: great vessels arise from the incorrect ventricle (i.e., ventriculoarterial discordance: aorta arises from the morphologic RV and PA arises from the morphologic LV) resulting in parallel circulations (Fig. 19-9a)
- **General**: most common cause of cyanotic CHD in neonates
- **Surgery**: adults with D-TGA have had some form of intervention in infancy including:
  - ■ Rashkind balloon atrial septostomy to allow sufficient mixing of deoxygenated and oxygenated blood and enable survival for the early post-delivery months
  - ■ Blalock Hanlon surgical atrial septectomy

- **Atrial switch**: **Senning and Mustard procedures (until 1980s)**—(Fig. 19-9b):
  - Re-routes systemic venous return to the MV and LV and lungs, and allows pulmonary venous flow to the TV and RV and aorta.
  - **Clinical exam**:
    - RVH with loud (single sounding) second heart sound from the anteriorly placed aorta, often no murmur
    - out flow murmur if there is associated sub pulmonic stenosis
    - holosystolic murmur if there is (systemic) TV regurgitation
  - **ECG**: marked right axis deviation and RVH (Fig. 19-9c)
  - **Echocardiography**: defines the status of the atrial baffle (rule out baffle leak or obstruction), rule out AV valvular regurgitation, presence of subpulmonic obstruction, and evaluate biventricular dysfunction.
  - **CT/MRI**: useful in diagnosing baffle leak or obstruction, and assessing ventricular volumes and function (Fig. 19-9d)
  - **Long term complications**:
    - Sinus node dysfunction, sudden death, atrial arrhythmias, ventricular arrhythmias
    - Atrial baffle leak allowing an atrial level shunt
    - Atrial baffle obstruction resulting in inhibition of systemic or pulmonary venous return
    - Systemic atrioventricular valve regurgitation and systemic RV dysfunction
  - **Management**:
    - Medications/ablation for atrial arrhythmias, pacemaker for significant sinus node dysfunction
    - Percutaneous intervention for both baffle leaks and obstruction
    - Systemic right ventricle failure with progressive TR should be managed with aggressive systemic afterload reduction but may require cardiac transplantation
- **Arterial switch: Jatene Procedure** (Fig. 19-9e)
  - Has largely supplanted the atrial switch procedure since the 1980s
  - Normal exam (healed incision) and generally normal ECG
  - Potential complications:
    - Aortic dilation and AR
    - Supra-aortic and supra-pulmonic anastomotic site stenosis
    - Coronary ostial obstruction (rare)
- **Congenitally corrected Transposition of the Great Arteries (CC-TGA, L-TGA, ventricular inversion)**:
  - Anatomy: systemic venous flow (vena cavae) enter the RA, traverse a MV to a subpulmonary LV and exit the PA to the lungs. The pulmonary veins enter the LA and traverse the TV to the RV to the aorta (making the TV the "systemic" ventricle).
  - Associated anomalies include VSD, pulmonic stenosis, or systemic AV valve (tricuspid) insufficiency (occasionally Ebstein-like valve) and complete heart block.
  - **Clinical exam**:
    - Consider L-TGA in any young adult with unexplained heart block
    - Loud second heart sound (from the anteriorly placed aorta)
    - Systemic AV valve insufficiency murmur (if tricuspid valve is abnormal or RV annulus is dilated)
    - If VSD and PS are present, there may be cyanosis and clubbing

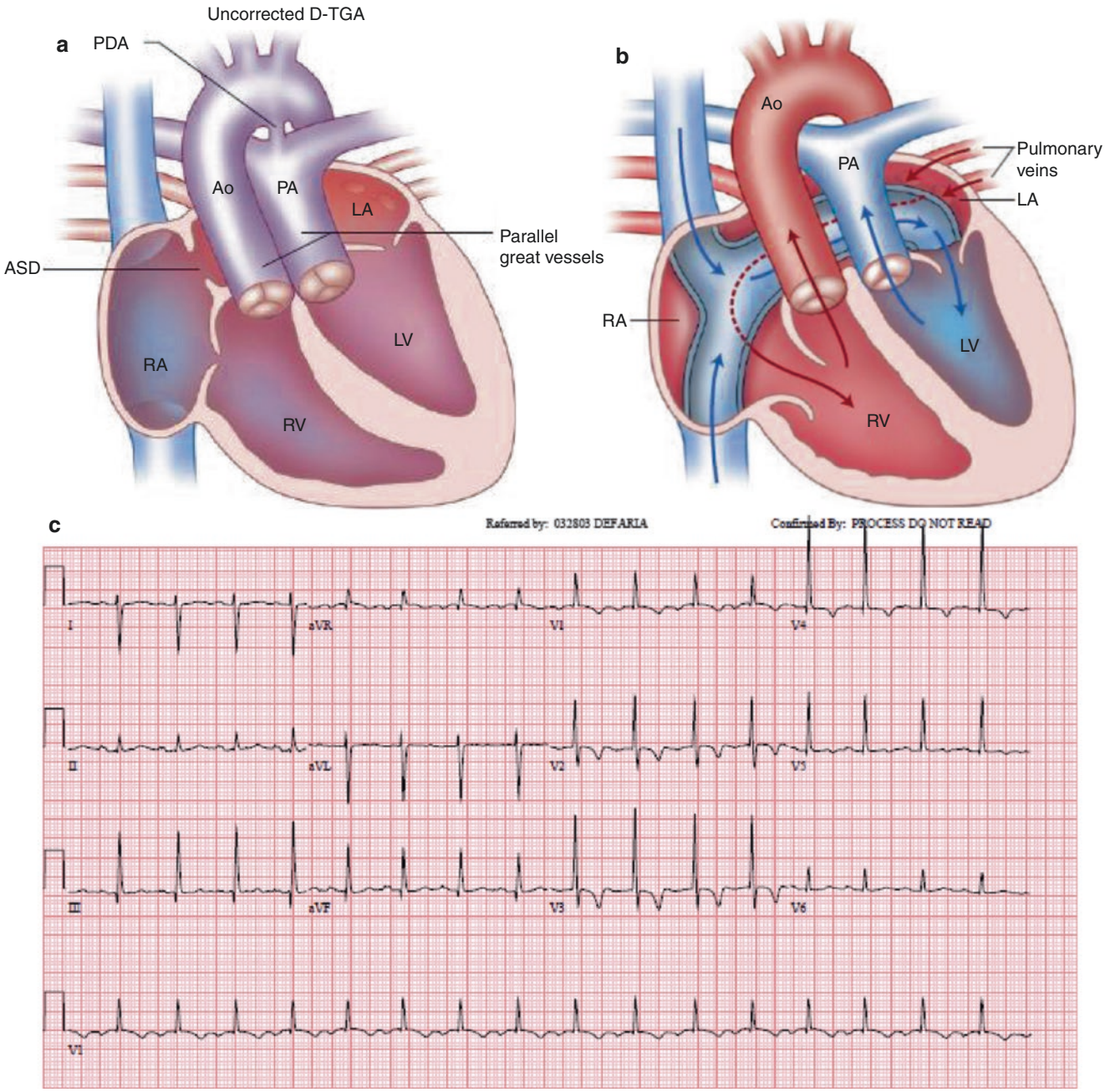


FIGURE 19-9

TGA. Transposition of the Great Arteries. (**a**) Schematic demonstrating parallel great vessels (D-TGA). (**b**) Schematic of Mustard anatomy with baffle directing SVC and IVC flow across the intraatrial septum to the morphologic right ventricle. (**c**) ECG with RVH and right axis deviation in a patient status post Mustard procedure (atrial switch). (**d**) CT angiography of great vessel relationship (D-TGA), note the aorta is anterior, axial imaging with patent intraatrial baffle directing flow from the pulmonary veins to the left atrium across the tricupis valve to hypertrophied systemic RV. (**e**) Schematic of Jatene arterial switch procedure

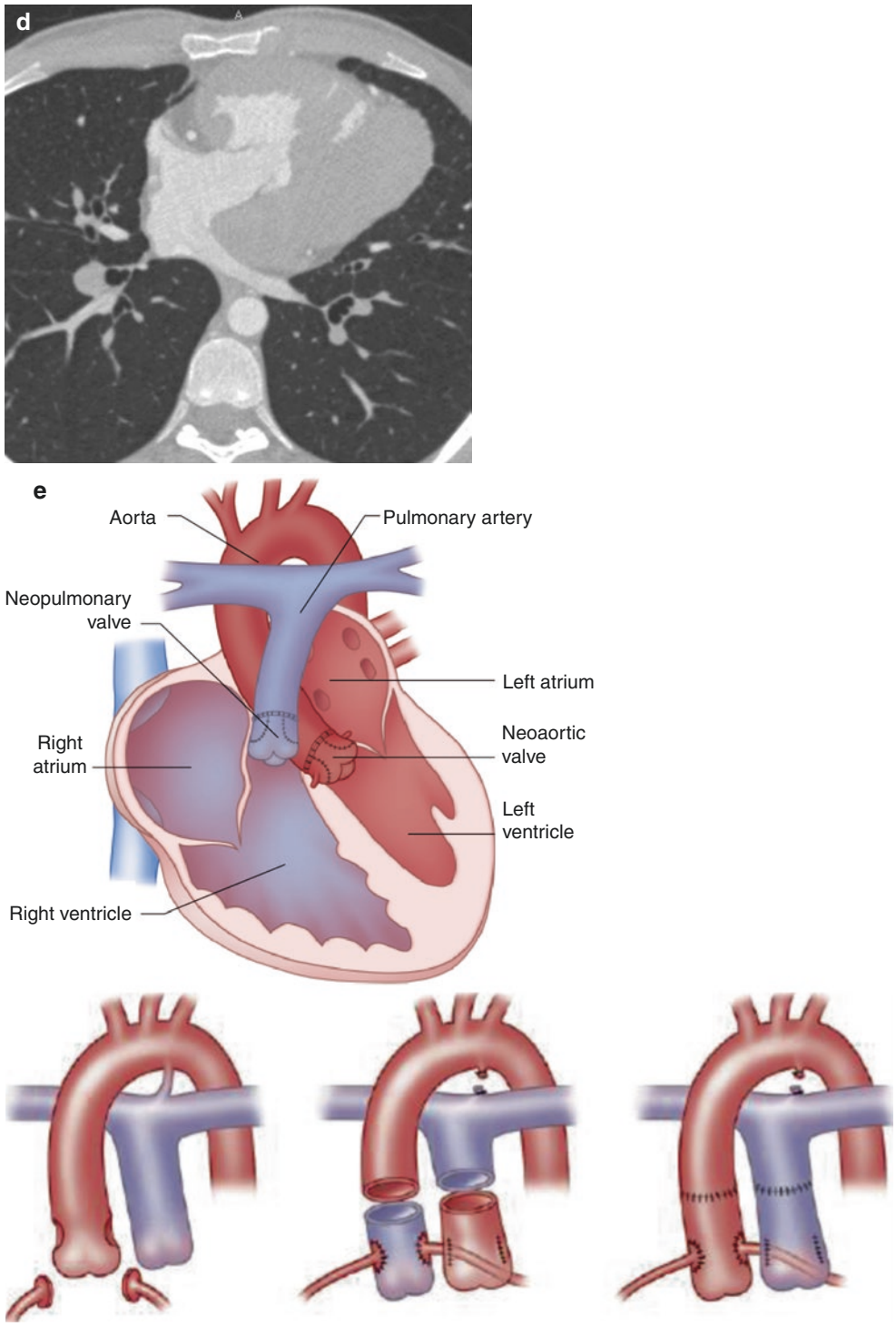


FIGURE 19-9

(continued)

– **ECG**: (Fig. 19-10a)
  - Classic ECG is diagnostic: Q wave in right precordial leads (septal depolarization direction is altered) with varying degrees of heart block
– **CXR**: (Fig. 19-10b)
  - Flat or convex upper left-sided cardiac silhouette, reflecting the abnormal ascending aorta position and take off

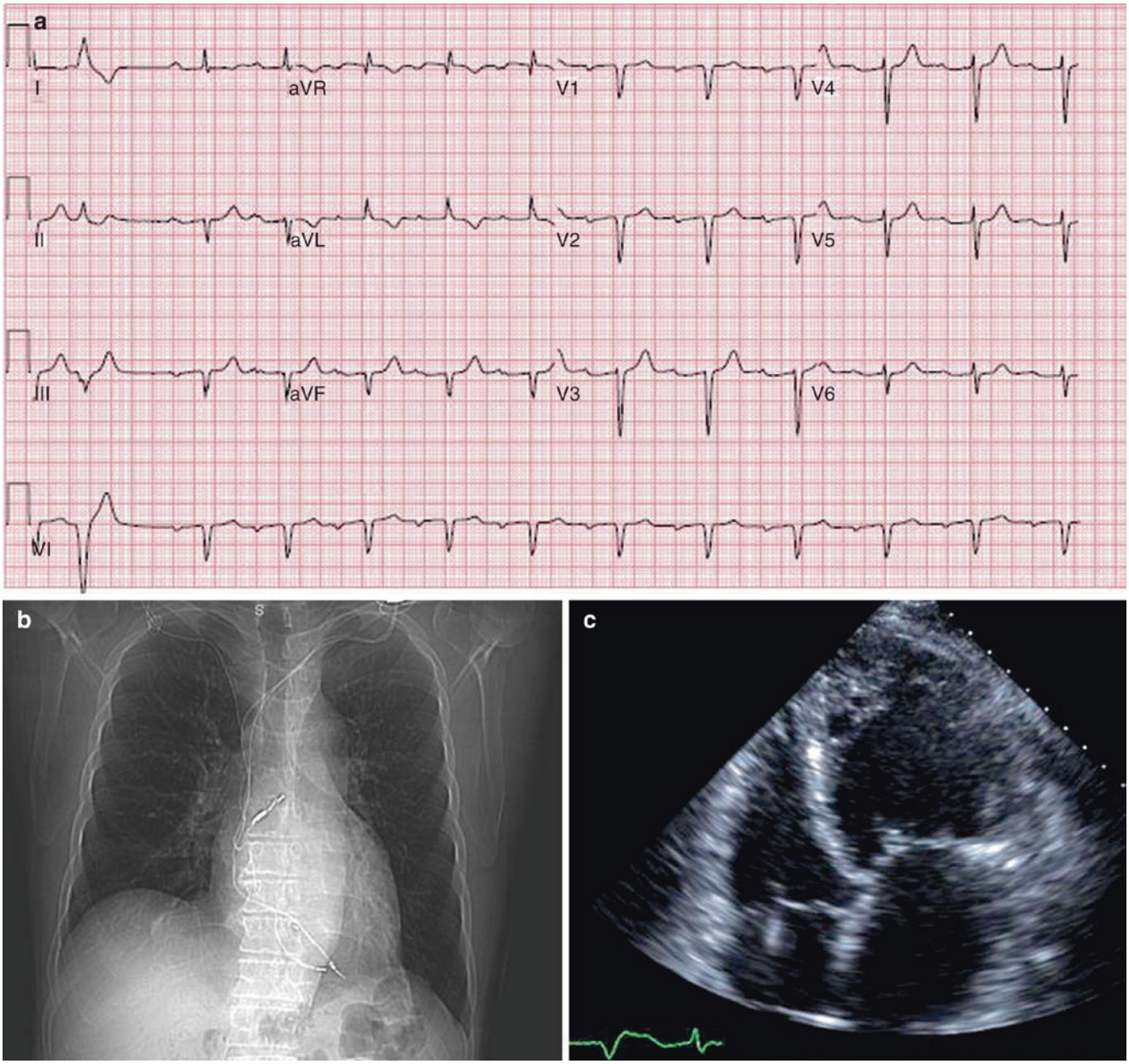


FIGURE 19-10

L Transposition of the Great Arteries. (**a**) ECG with first degree AV block, Q waves in II, III, aVF, absence of septal Q waves in V5-V6 due to inversion of the right and left bundle branches causing septal activation to occur from right to left axis deviation and PVC not necessarily seen in L-TGA. (**b**) CXR of patient with L-TGA and dual chamber pacer. (**c**) four-chamber view demonstrating apical displacement of the systemic AV valve indicating this is a tricuspid valve and systemic right ventricle, pacer lead also noted in the morphologic (subpulmonary) LV

- **Echocardiogram**: (Fig. 19-10c)
  - Gold standard for diagnosis and detection of associated lesions.
  - Apically placed TV which enters the RV receives LA inflow and communicates with the aorta. Apical 4 chamber best demonstrates the "inverted ventricles".
- **Outcomes**:
  - May survive well into older age with essentially normal lifestyle including pregnancy and delivery.
  - Complete heart block may require pacemaker placement (active fixation leads may be needed for the smooth LV septal surface.
  - Can present with progressive systemic (tricuspid) AV valve regurgitation and progressive systemic RV dilation, dysfunction and failure
- **Management**:
  - Afterload reduction and maintaining lower blood pressure is helpful
  - Pacemakers for complete heart block, small studies reveal cardiac resynchronization may have a role in some patients with systemic RV failure.
  - TV replacement (less often repair) for significant TR if systemic ventricular function is not severely compromised may help preserve systemic ventricular function.
  - Clinical management of L-TGA patients can be challenging and expert ACHD input is strongly recommended.
  - Cardiac transplantation may be needed for medically refractory heart failure.

Univentricular Heart and Fontan Revision (Fig. 19-11**)**
(Tricuspid or Mitral atresia, hypoplastic left or right heart syndrome)

- **Early Interventions include**:
  - Pulmonary artery banding: protect the lungs from overcirculation for patients with no natural pulmonary flow obstruction
  - Modified Blalock-Taussig shunt (subclavian artery to PA prosthetic conduit): often used for infants with severe pulmonic stenosis or pulmonary atresia and cyanosis, and staged prior to the Fontan procedure
  - Glenn procedure: direct connection of SVC to right PA (may cause late right pulmonary arteriovenous malformations—secondary to absence of inferior venous cava flow to the right lung which may carry "liver factors" which prevent pulmonary arteriovenous malformation)
- **Fontan procedure**: allows systemic venous flow to be directed to the lungs without the aid of a ventricular pump (Fig. 19-11).
  - **Complications**:
    - RA to PA Fontan: RA enlargement, thrombus formation, atrial arrhythmias, hepatic congestion and eventual cirrhosis
    - Lateral tunnel Fontan: Atrial arrhythmias, hepatic congestion
    - Extracardiac conduit: Hepatic congestion may still occur
    - Fistulous communications from the systemic to the pulmonary circulation may present as new onset progressive desaturation, often amenable to transcatheter occlusion
    - Univentricular dysfunction as well as AV incompetence may be progressive in adult life, hence early and continued management with afterload reduction and avoidance of systemic hypertension is an essential feature for these patients.
  - When Fontan patients require intubation avoidance of positive pressure is essential
- **Pregnancy**: can be very challenging, contraindicated in severe cyanosis, may not do well with depressed single ventricle ejection fraction

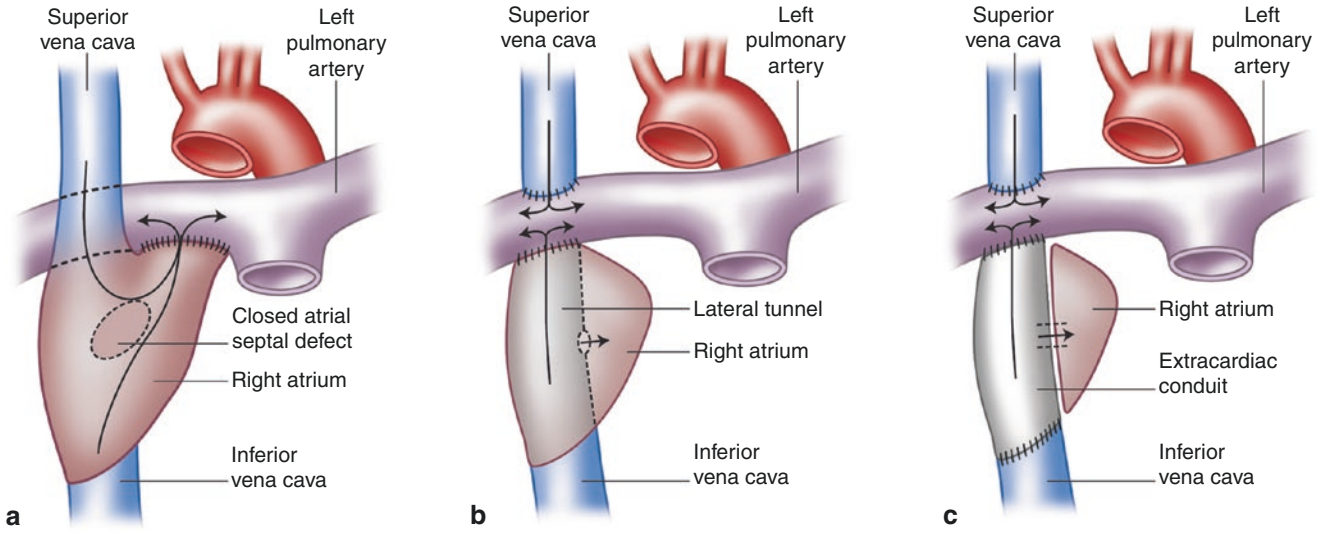


FIGURE 19-11

Fontan procedure

Eisenmenger Syndrome

- **General**: seen in patients with large left-to-right shunt lesions who were not appropriately intervened upon in childhood (generally because of limited access to health care); defined as progressive increase in PVR which leads to reversal of shunting (right-to-left) and ultimately subpulmonary ventricular failure and death; overall, increasingly uncommon
- **Clinical Exam**:
  - Cyanosis, clubbing, jugular venous a wave
  - Prominent RV heave, loud P2
  - Often no murmur, but occasionally the holosystolic murmur of TR or diastolic murmur of functional PR from elevated PVR
  - Hepatosplenomegaly from chronic congestion
- **CXR**: Large main PA and central PA with oligemic periphery (pruning) (Fig. 19-12a, b)
- **Complications**:
  - Systemic emboli or abscess from right-to-left shunting
  - Erythrocytosis as a response to chronic hypoxemia, thrombocytopenia from splenic sequestration; neurologic events may occur due to hyperviscosity syndrome
  - Hemoptysis may occur
  - Arrhythmia and sudden cardiac death
- **Management**: Medical therapy with pulmonary arterial vasodilators is an option and may prolong survival [4] and the only surgical option is heart-lung transplant. ACC/AHA Class I recommendations:
  - Avoidance of dehydration, moderate to severe strenuous activity, isometric exercise, excessive heat, chronic high altitude exposure and iron deficiency [2]
  - Annual monitoring of hemoglobin, platelet count, iron stores, creatinine, and uric acid annually; assess oximetry with and without oxygen annually [2]
  - Right-to-left shunt precautions are essential with all IVs [2]

Other recommendations: Endocarditis prophylaxis, phlebotomy when appropriate (neurologic symptoms from hyperviscosity), anticoagulation may be considered, avoidance of unessential surgery or anesthesia is important. With appropriate and experienced clinically guided care, Eisenmenger patients can survive to midlife and on occasion beyond

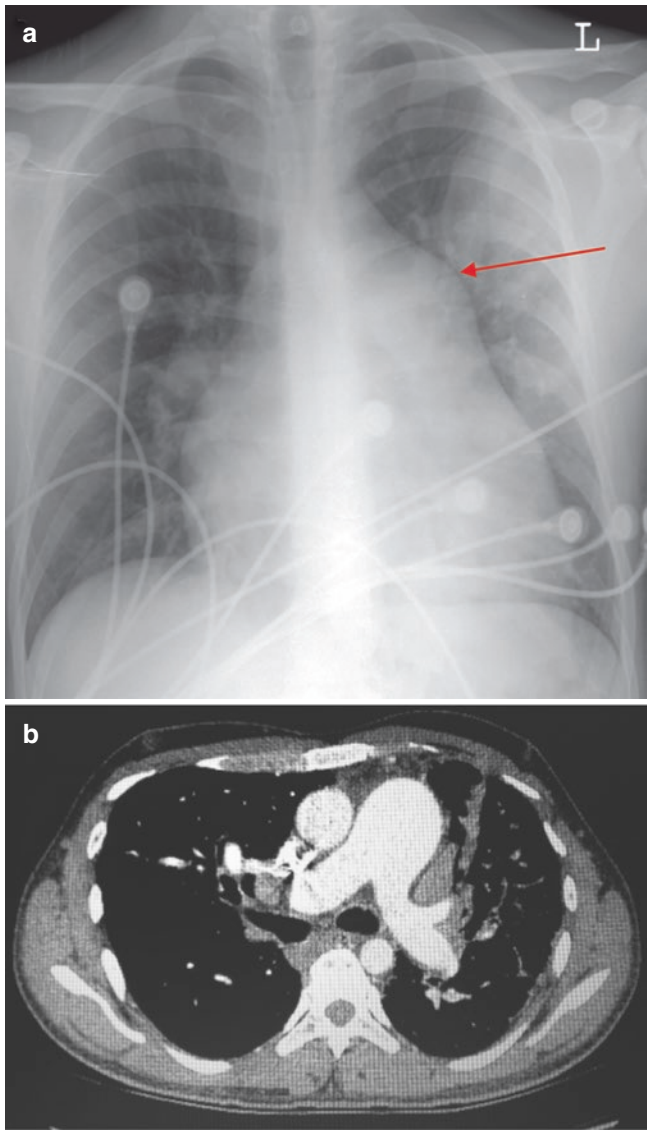


FIGURE 19-12

Eisenmengers syndrome. (**a**) CXR with prominent pulmonary artery (arrow) in an Eisenmengers patient. (**b**) CT angiography with enlarged pulmonary artery (larger than aorta) and branches

■ **Pregnancy**: strictly contraindicated

Dextrocardia and Cardiac Malposition

■ **Mirror Image Dextrocardia**: (Fig. 19-13a)

- Total situs inversus: heart chambers and body viscera are all in mirror image position
- Many have no associated congenital cardiac anomaly
- ECG, Echo, CXR: when present, can trigger identification (Fig. 19-13b)

■ **Kartagener's syndrome**:

- Bronchiectasis, sinusitis, ciliary dysmotility, infertility
- Limited to those with mirror image dextrocardia and not seen in dextroversion (heart is dextrorotated but visceral abdominal organs are in normal position)

Congenital Coronary Anomalies (Fig. 19-14)

■ **ALCAPA**: anomalous left coronary artery origin from the PA (rare)

- In the absence of surgical intervention, most infants die in early infancy. Rare natural survivors may have acute myocardial infarction (MI), MR and LV failure and survive to childhood.

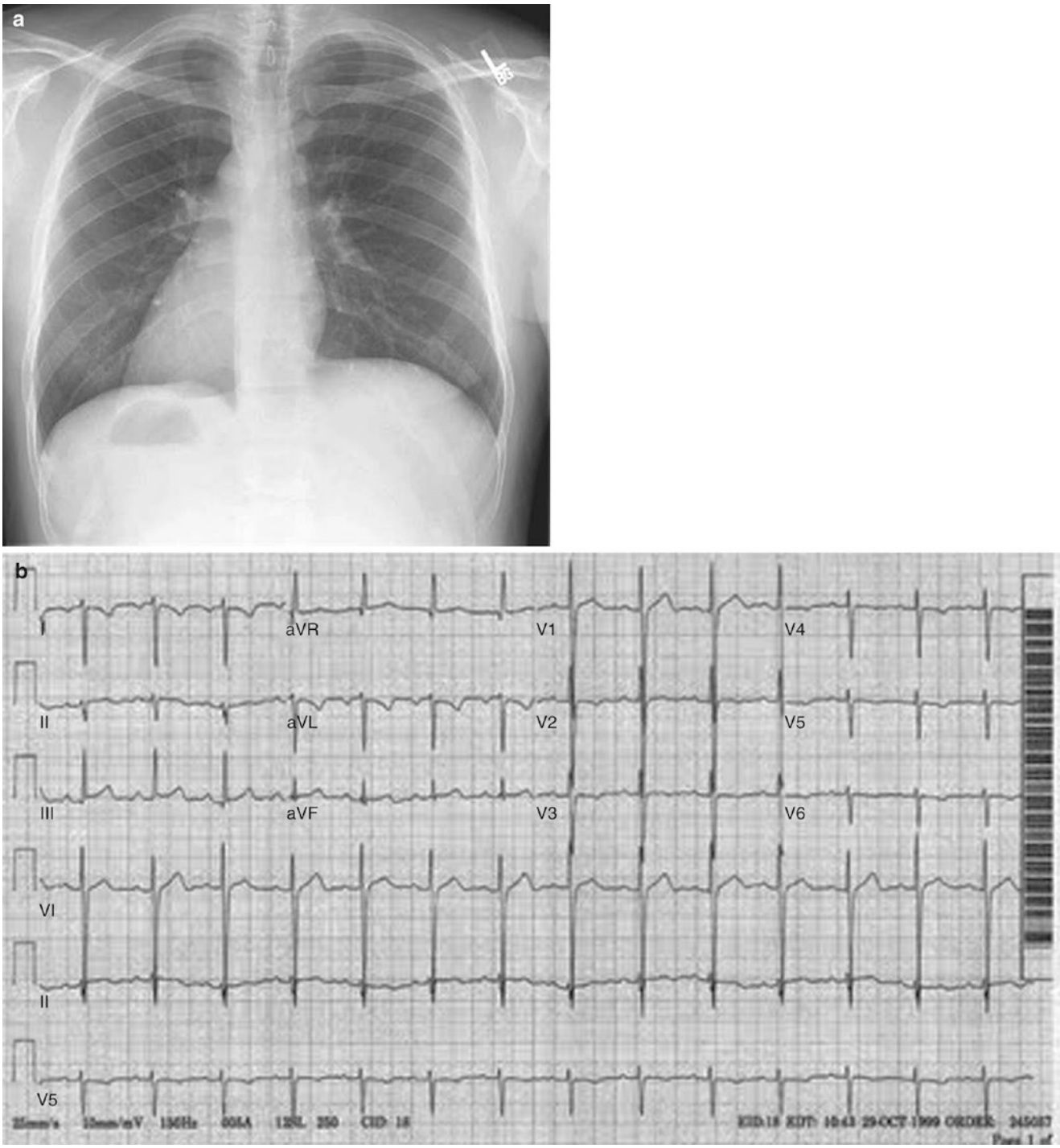


FIGURE 19-13

Dextrocardia. (**a**) CXR of classic mirror image dextrocardia (note that stomach bubble is on the patient's right). (**b**) ECG (with typical lead placement) of dextrocardia demonstrating inverted R progression, negative P wave and right axis deviation. Differential diagnosis for negative P wave in lead I includes: right/left arm reversal or mirror image dextrocardia

- **Management in Infancy involves**:
  - Creation of a tunnel in the posterior PA to redirect the anomalously arising left coronary artery blood flow to a neo left coronary ostium and the left coronary artery.
  - Long term results of this procedures are still evolving but are encouraging with near normal LV function.
  - Even in patients who had significant LV damage with their presentation as infants, LV recovery often seems very favorable.
  - Exercise treadmill testing with imaging, arrhythmic monitoring and in many beta blockade or angiotensin converting enzyme (ACE) inhibition for less than normal LV function is likely prudent.
- **Adult presentation**:
  - Infants can grow to adulthood with minimal complications and no significant heart failure post repair
  - Approximately 5% of ALCAPA patients are unrepaired and survive by natural intercoronary collateral flow and may present in adult life with a palpable left ventricular aneurysm, MR, ventricular tachyarrhythmia and a continuous flow bruit over the anterior wall from the right to the left coronary circulation
  - ECG: may demonstrate LV aneurysm or remote anterior myocardial infarction pattern (Q waves and ST changes with loss of R waves in the anterior precordial leads).

- **Ectopic origin of the coronary artery**:
  - Either the left or right coronary artery may arise from the contralateral sinus of Valsalva and pass anteriorly to the aorta and posterior to the RV out flow tract. Other coronary anomalies include a single coronary orifice, an aberrant LAD (in TOF arising from the RCA) or aberrant left circumflex (usually from the right, retroaortic, and therefore benign) (Fig. 19-14a, b)

- **Presentation of anomalous coronary from contralateral cusp**:
  - Incidental finding during scan for alternate indication
  - Sudden cardiac death
  - Ventricular arrhythmia
  - Exertional chest symptoms or syncope

- **Diagnosis**:
  - Targeted ultrasound of coronary artery origins can be diagnostic (parasternal short axis above the level of the aortic valve)
  - MRI and CTA can be confirmatory (define the course of the vessel, assess for dominance of the artery and caliber of the proximal lumen and of the ostium. CT can assess for atherosclerosis which can change a previously benign clinical presentation)

- **High risk features**:
  - Age at presentation <50 years
  - Proximal hypoplasia and stenosis of the ectopic artery, or proximal oblique (or 'slit-like') orifice
  - Interarterial course: anterior to the aorta and posterior to the RVOT alone may not be the strongest risk factor, however the presence of a dominant ectopic vessel with proximal anatomic or functional obstruction suggests high risk and surgical intervention should be considered. Individuals with an interarterial course alone and age >50 years have anecdotally survived well with no intervention.
  - Presentation with ventricular arrhythmia in adolescence or young adulthood especially with exertion.
  - Presence of detectable ischemia on stress testing in the distribution perfused by the ectopic artery

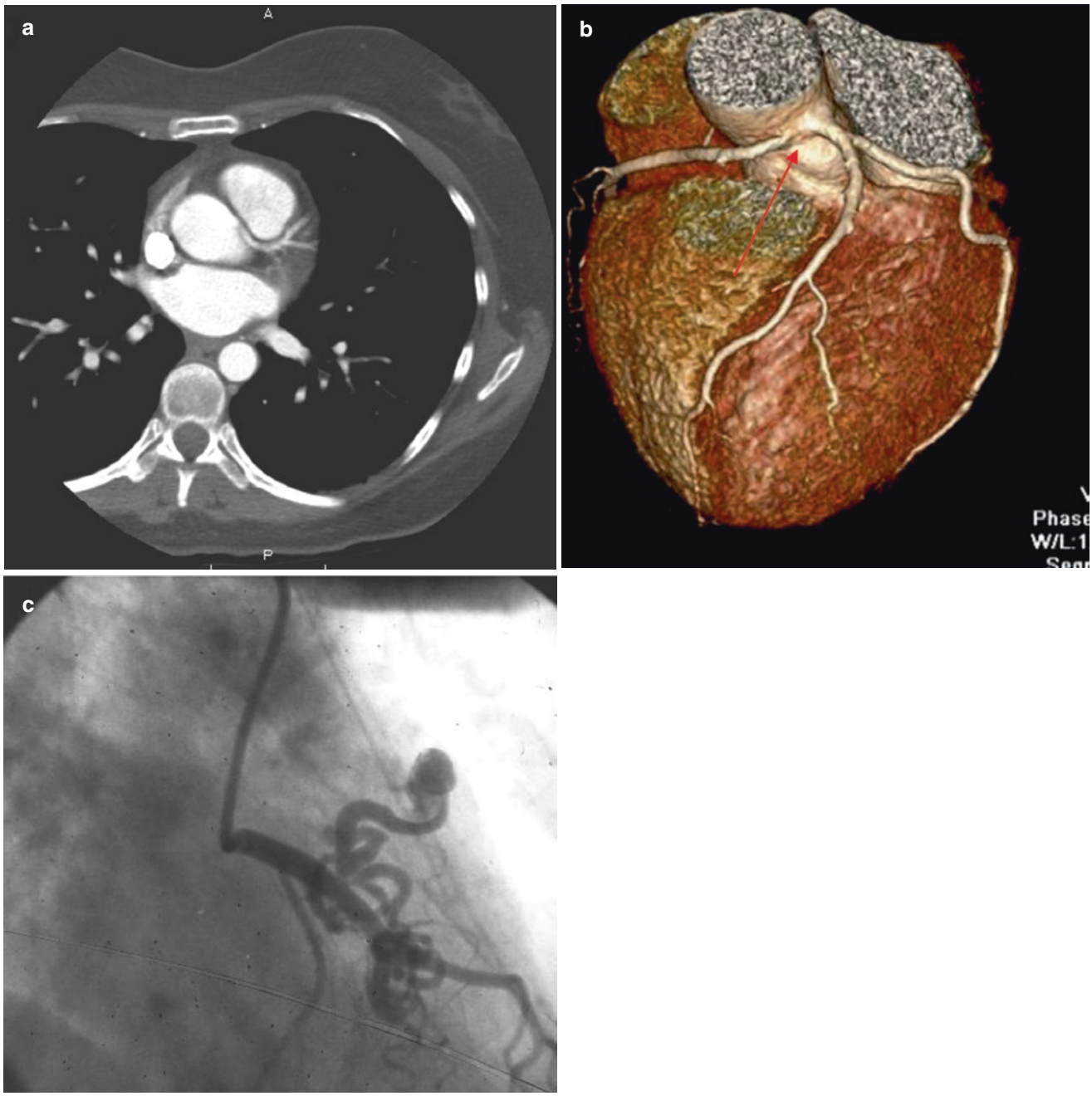


FIGURE 19-14

Anomalous coronary arteries and coronary AV fistula. (**a**) Anomalous left anterior descending arising from the right coronary cusp with posterior course (traversing between the aorta and the RVOT). (**b**) Anomalous right coronary artery arising from the left coronary cusp (arrow) with anterior course, note all coronaries originate off the left coronary cusp. (**c**) Angiography of congenital coronary AV fistula from left main to pulmonary artery, often times small and tortuous and rarely need intervention

■ **Management**:

- Without high risk features: beta blockade (data are limited) and lifestyle modification
- With high risk features: beta blockade and consider surgical revascularization
- Anomalous coronary artery assessment and management can be challenging and expert ACHD consultation (with multidisciplinary evaluation) is often prudent.
- ACC/AHA Class I recommendations (Level of Evidence B): surgical revascularization if:

- anomalous left main courses between the aorta and PA/RVOT
- documented ischemia due to coronary compression
- anomalous origin of the right coronary between the aorta and PA/RVOT with evidence of ischemia [2]

- **Congenital coronary AV fistula**: (Fig. 19-14)
  - **Clinical exam**: (in larger congenital coronary AV fistula)
    - Precordial continuous murmur (see differential above under PDA, physical exam)
  - **Presentation**:
    - Subclinical, incidental fi n dings by ultrasound or at the time of coronary angiography (particularly small left main to PA congenital coronary AV fistula—Fig. 19-14c)
    - Heart failure, cardiomegaly (when large, usually from RCA or left circumflex, entering right heart)
    - Thrombosis
    - Ischemia secondary to steal phenomenon, where the fistula redirects flow away from the coronary distal to the fistula takeoff
  - **Management**:
    - Observation for small fistulas
    - If amenable, transcatheter coils are the treatment of choice
    - Surgical approach is also an option in select cases, and preferable with large aneurysms (Figs. 19-15, 19-16, 19-17, and 19-18) (Table 19-2).

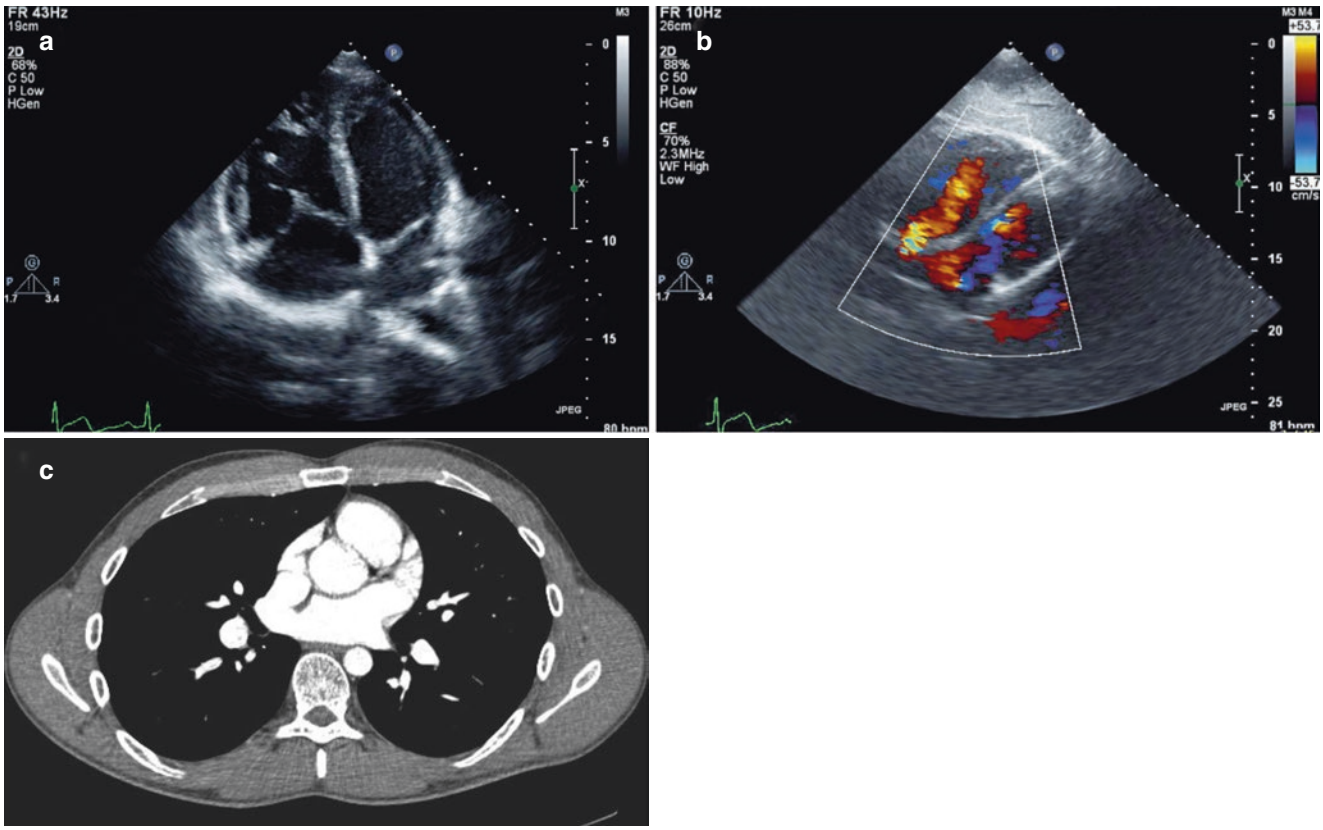


FIGURE 19-15

Question 1

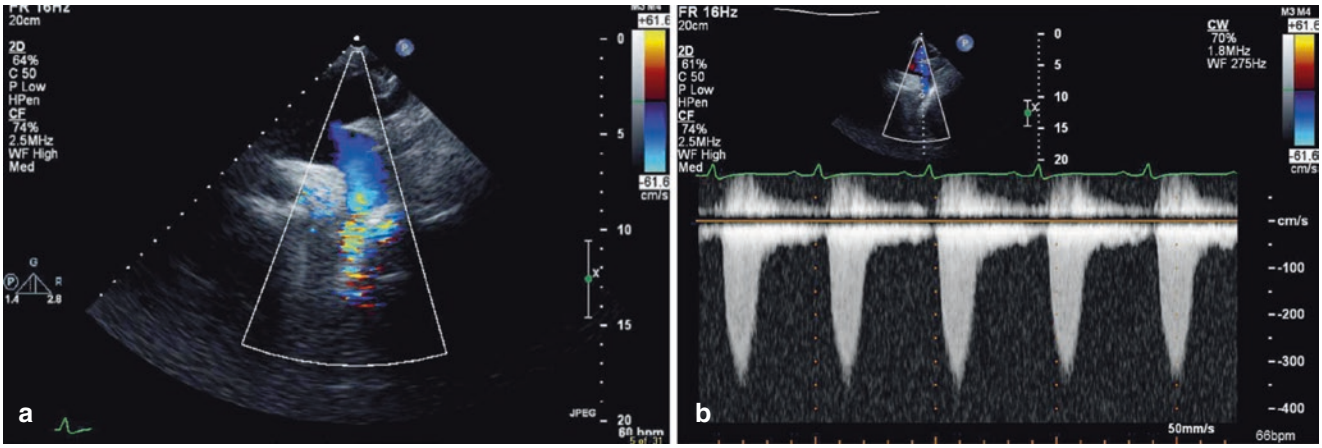


FIGURE 19-16

Question 2

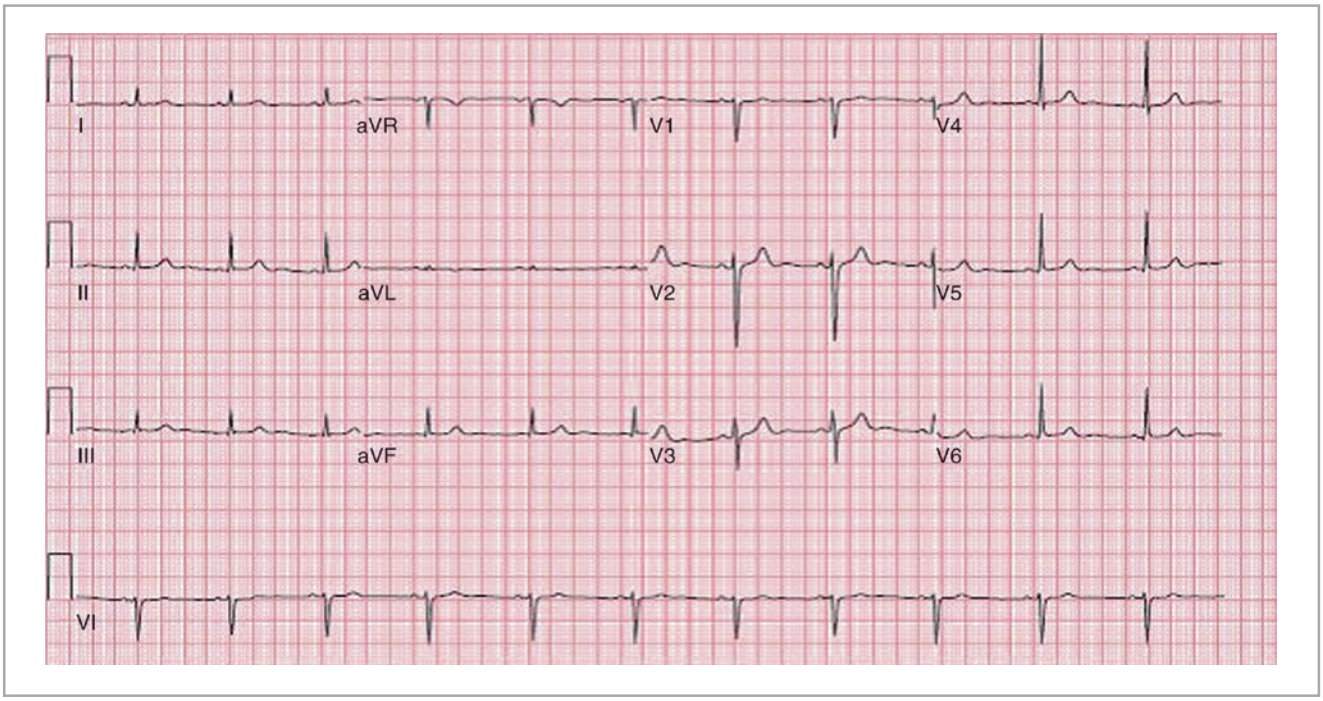


FIGURE 19-17

Question 4

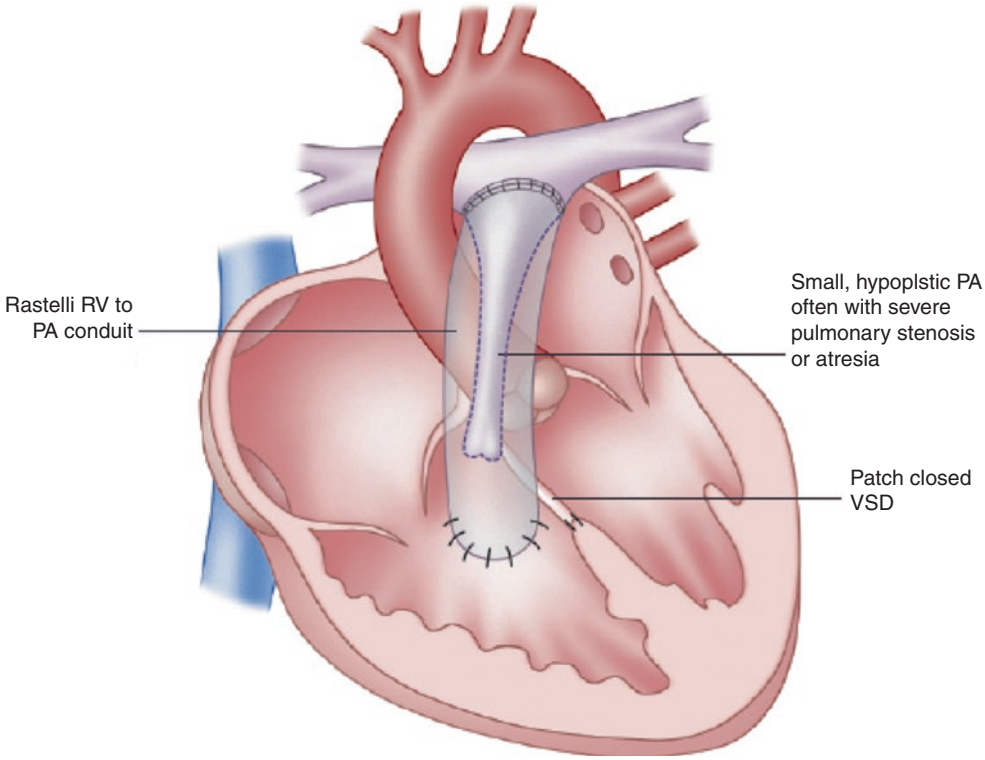


FIGURE 19-18

Rastelli

TABLE 19-2

SYNDROMES ASSOCIATED WITH CONGENITAL HEART DISEASE

SYNDROME	DESCRIPTION	ASSOCIATED CONGENITAL LESIONS
Holt Oram	Congenital abnormality of the hand and radius; autosomal dominant	Atrial septal defect
Williams Syndrome	Deletion of elastin gene (7q11.23)	Supra aortic stenosis
Noonan Syndrome	Facial dysmorphism, short stature; autosomal dominant	Pulmonic stenosis/dysplasia, hypertrophic cardiomyopathy, pectus excavatum
Down Syndrome	Trisomy 13, intellectual disability	AV canal defects (45%), VSD (35%), PDA 7%, TOF 4%
Turners Syndrome	45× karyotype; Females; gonadal dysgenesis; short stature, primary amenorrhea	Aortic valvular disease (20–30%) and aortic coarctation (3–10%)
Congenital Rubella Syndrome	Hearing impairment, cataracts/ congenital glaucoma, retinopathy	PDA, branch pulmonary stenosis
Peutz Jaeger syndrome	Autosomal dominant; intestinal polyps	PDA

QUESTIONS AND ANSWERS

A 78-year-old male with a past medical history significant for a 40 pack-year smoking history, atrial fibrillation and coronary artery disease status post placement of drug eluting stent to an occluded left circumflex artery approximately 10 years prior presented with new shortness of breath on exertion, particularly on hills and stairs, and minimal abdominal bloating and lower extremity edema over a 3-week period. He denied chest pain, paroxysmal nocturnal dyspnea, orthopnea, palpitations, or syncope. Prior cardiac catheterization 10 years prior also demonstrated minimal disease in the left anterior descending artery and right coronary artery with a normal left ventricular ejection fraction. On exam he had normal vital signs including oxygen saturation. Cardiac exam was remarkable for Normal S1 with prominent and fixed splitting of the S2, jugular venous distention to the angle of the jaw with hepatojugular reflex and a 2/6 holosystolic murmur at the right sternal border and mild pedal edema.

Transthoracic echocardiogram demonstrated significant right ventricular enlargement with moderate RV dysfunction and left ventricular dysfunction with an ejection fraction of 47% (55% on study 1 year prior) as well as a large sinus venosus septal defect with left to right shunt. Patient was started on guideline-directed medical therapy for HFrEF and chemical nuclear stress test revealed a markedly enlarged right ventricle (RV) but no ischemia.

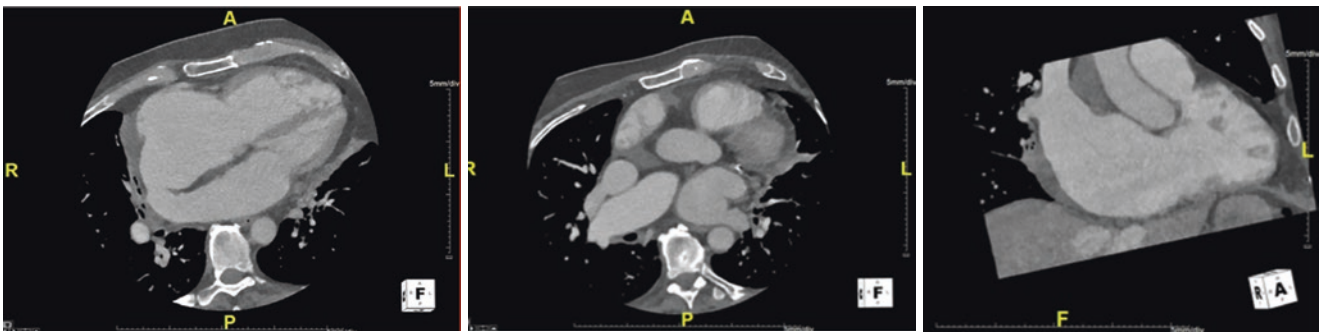
Question 1: What other congenital anomalies are associated with sinus venosus ASD?

A. Partial anomalous pulmonary venous connection
B. Cleft mitral valve
C. Ventricular septal defect
D. Holt-Oram syndrome

Answer: A

A. Partial anomalous pulmonary venous return is associated with sinus venosus septal defects and should be diagnosed prior to surgical repair.
B. Cleft mitral valve is usually seen with primum atrial septal defects, associated often with a right bundle branch block and left axis deviation on EKG.
C. Ventricular septal defects are one of the most common non-cyanotic congenital heart diseases, not usually associated with sinus venosus septal defects.
D. Holt-Oram Syndrome is associated with secundum atrial septal defect

CTA revealed sinus venosus septal defect (A), enlargement of pulmonary arteries (B), and PAPVR (C).



Question 2: What is the recommended modality for sinus venosus septal defect closure?

A. Primary catheter-based percutaneous intervention
B. Primary Surgical repair
C. No intervention indicated, this is a left heart problem

Answer: B

A. Sinus venosus defects cannot be closed at this time with percutaneous devices because of insufficient tissue for adequate landing of device. The patient underwent repair of the sinus venosus ASD and PAPVR using double pericardial patch technique with TVR #33 St. Jude Medical Biocor porcine valve, modified MAZE procedure, left atrial appendage clipping (Atriclip 45 mm), and placement of permanent epicardial pacemaker.
B. These patients require primary surgical repair to prevent the known risk of forming right ventricular dilation and dysfunction and associated atrial arrhythmia.
C. There is no ischemic LV disease at this time, and the size and dysfunction of the RV may influence the LV through ventricular ventricular interactions. After surgical repair, this patient's LV function returned to normal as the RV size and function improved.

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CHAPTER 20

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Aortic and Pulmonic Valvular Heart Disease

CHAPTER OUTLINE

ABBREVIATIONS

AR	Aortic regurgitation
AS	Aortic stenosis
AV	Aortic valve
AVA	Aortic valve area
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
CAD	Coronary artery disease
DSE	Dobutamine stress echocardiography
EF	Ejection fraction
ETT	Exercise treadmill test
HF	High flow
HG	High gradient
LF	Low flow
LG	Low gradient
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MDCT	Multidetector computed tomography
NF	Normal flow
PPVI	Percutaneous pulmonic valve implantation
PR	Pulmonic regurgitation
PS	Pulmonic stenosis
RV	Right ventricular
SAVR	Surgical aortic valve replacement
SV	Stroke volume
SVi	Stroke volume index
TAVR	Transacather aortic valve replacement

AORTIC STENOSIS (AS)

Etiology

- Aortic stenosis (AS) is present in 12.4% percent of adults > 75 years of age, of which 3.4% have severe AS. The prevalence of AS is projected to continue to increase due to the aging population and absence of therapies to halt its progression [1].
- The most common cause of AS is calcific degeneration [2].
- Calcific AS was historically felt to be due to age-related degeneration; however, it is due to an active process similar to atherosclerosis that includes lipid deposition, inflammation, and active calcification [3–7]. Severe AS most frequently presents in the sixth to seventh decades of life.
- Bicuspid aortic valve disease occurs in 1–2% of the general population and is a strong risk factor for the development of AS.
  - Bicuspid aortic valves (AV) occur more frequently in men (about 2:1) than in women.
  - Severe AS due to a bicuspid AV can occur earlier in life as compared to with a trileafet AV, most commonly presenting in the fifth and sixth decades of life [8, 9].
- Rheumatic AS rarely occurs in the Western world and is most often associated with concomitant mitral pathology.

Pathophysiology and Hemodynamics

- AS is a progressive disease with stages of disease defined by valve anatomy, valve hemodynamics, and symptomatology.
  - Stage A: Bicuspid AV or AV sclerosis identified, at risk for AS.
  - Stage B: Mild to moderate AS (see Table 20-1).
  - Stage C: Hemodynamically significant AS without symptoms.
  - Stage D: Hemodynamically significant AS with symptoms.
  - LV hypertrophy occurs in order to maintain normal wall stress (σ) which is proportional to the LV pressure (P) and radius (r) and inversely related to wall thickness (T) as dictated by LaPlace's law: $\sigma = (P * r)/2T$.
  - Normalization of wall stress is a compensatory mechanism that initially preserves LV contractile function.
  - Progressive AS leads to progressive LV hypertrophy, increased LV systolic pressure and increased LV ejection time, all of which result in increased myocardial oxygen demand. Simultaneously, LV diastolic pressure is increased, aortic pressure is decreased, and diastolic filling time is decreased, resulting in decreased myocardial oxygen supply. The increased myocardial oxygen demand and decreased myocardial oxygen supply lead to myocardial ischemia and ultimately LV failure.

TABLE 20-1

SEVERITY OF AORTIC VALVE STENOSIS

	AORTIC SCLEROSIS	MILD	MODERATE	SEVERE
Aortic jet velocity (m/s)	≤2.5	2.6–2.9	3.0–4.0	≥4.0
Mean gradient (mm Hg)	–	<20	20–40	≥40
AVA (cm^2)	–	>1.5	1.0–1.5	≤1.0
Indexed AVA (cm^2/m^2)		>0.85	0.60–0.85	≤0.6
Velocity ratio		>0.50	0.25–0.50	<0.25

Adapted from [10, 11]

- High-gradient, severe AS is defined by the following echocardiographic criteria:
  - Peak aortic jet velocity ≥4 m/s or mean transvalvular pressure gradient ≥40 mm Hg and,
  - Aortic valve area (AVA) ≤1.0 cm^2 or, if indexed, ≤0.6 cm^2/m^2 [10].
- Low-gradient (LG) AS is defined by a mean transvalvular pressure gradient < 40 mmHg and an AVA ≤ 1.0 cm^2 or ≤0.6 cm^2/m^2. Based on differences in echocardiographic measurement of transvalvular flow and LV ejection fraction, different subtypes of low-gradient AS have been described.
  - Low-flow (LF) is defined as a stroke volume index (SVi) <35 mL/m^2, while normal-flow is defined as an SVi ≥ 35 mL/m^2. LF may result from various causes, such as reduced LV systolic contractile function or adverse LV remodeling resulting in a small volume LV cavity.
  - Left ventricular ejection (LVEF) ≥ 50% is considered normal and < 50% is low.
- Subtypes of LG AS
  - Low-flow, low-gradient aortic stenosis (LF-LF AS) with reduced LVEF, i.e., "classical" LF-LG AS: 5–10%
    - AVA ≤1.0 cm^2 or ≤0.6 cm^2/m^2, mean transvalvular pressure gradient <40 mm Hg, impaired LVEF (<50%) leading to LF (SVi <35 mL/m^2).
  - Low-flow, low-gradient aortic stenosis (LF-LG AS) with normal LVEF, i.e., "paradoxical" LF-LG AS: 10–25%
    - AVA ≤1.0 cm^2 or ≤0.6 cm^2/m^2, mean transvalvular pressure gradient <40 mm Hg, and normal LVEF (≥50%).
    - Characterized by pronounced LV concentric remodeling, small LV cavity size, restrictive physiology leading to reduced LV outflow characterized by LF and LG [12].
  - Normal-flow, LG aortic stenosis: 15–40%
    - AVA ≤1.0 cm^2 or ≤0.6 cm^2/m^2, mean transvalvular pressure gradient <40 mm Hg, with normal flow (SVi >35 mL/m^2).

Assessment

History (See Chap. 1 for Important Details)

- AS is typically asymptomatic until valvular stenosis is severe. However, up to 50% of patients with severe AS are asymptomatic [13].
  - Symptom development in a patient with moderate to severe AS may also suggest the presence of underlying coronary artery disease (CAD).
- The hallmark of AS is the classical triad of exertional dyspnea, angina, and syncope (or near-syncope).
  - Exertional dyspnea is the most common symptom associated with severe AS.
  - Angina without significant obstructive CAD is caused by subendocardial ischemia due to increased total oxygen demand secondary to increased LV mass and reduced coronary perfusion pressures in the setting of elevated LV diastolic pressures. Up to 1/2 of patients with severe AS will also have underlying CAD.
  - Exertional syncope (or near syncope) occurs due to diminished cerebral perfusion secondary to peripheral vasodilation in the presence of a fixed cardiac output resulting in hypotension.
  - These symptoms do not develop simultaneously, and in many cases, only one of the three is present.

Physical Examination (See Chap. 1 for Important Details)

- Hallmarks of severe AS on physical examination include:
  - Reduction in the amplitude and delay of the carotid upstrokes ("parvus et tardus")
  - Diminution or entire loss of the second heart sound
  - Late peaking systolic crescendo-decrescendo murmur
- The murmur of AS radiates to the carotids, sometimes associated with a thrill.
  - Radiation may also occur across the precordium and to the apex (Gallavardin phenomenon) associated with a musical, high frequency quality.
- The murmur increases with squatting, decreases with standing
  - This helps to differentiate it from hypertrophic obstructive cardiomyopathy.
- Other findings include an opening click in patients with a bicuspid valve, as well as the murmur of AR.

Echocardiography

- Transthoracic Doppler echocardiography is the standard method for quantifying the degree of AS (Table 20-1).
- The velocity (V) across the stenotic AV on echocardiography can be used to estimate the peak pressure gradient across the valve (ΔP) by use of the Bernoulli equation:
  - $\Delta P = 4V^2$
- The principle of conservation of mass dictates that flow within the left ventricular outflow tract (LVOT) must be the same as flow through the aortic valve (AV). Hence, AVA can be calculated using the continuity equation:
  - $AVA * VTI_{AV} = CSA_{LVOT} * VTI_{LVOT}$

  Therefore,
  - $$AVA = \frac{CSA_{LVOT} * VTI_{LVOT}}{VTI_{AV}}$$

  where VTI is the velocity time integral and CSA is cross sectional area.
- Hemodynamically severe AS is defined as:
  - Peak aortic jet velocity ≥4 m/s or a mean transvalvular pressure gradient ≥40 mm Hg OR
  - AVA ≤1.0 cm^2 or ≤0.6 cm^2/m^2 indexed for body surface area [10].
- LF is characterized as stroke volume index < 35 ml/m^2 measured in the LV outflow tract by Doppler echocardiography [12].

Exercise Stress Testing [14]

- Exercise treadmill testing (ETT) is recommended (Class IIa) in patients with asymptomatic severe AS to evaluate for un-recognized AS-related symptoms and risk stratify the timing of aortic valve replacement (AVR).
  - Limiting symptoms (dyspnea, angina, syncope) on ETT are an indication (Class I, Level of Evidence A) for AVR [10].
  - Decreased exercise tolerance, abnormal systolic blood pressure response (drop or < 20 mm Hg rise) are poor prognostic factors, AV intervention can be considered (Class IIa) [13].

Cardiac Catheterization

- Invasive assessment of AS severity is recommended when noninvasive tests are inconclusive or discordant with clinical findings [15].
- During cardiac catheterization, the mean gradient across the aortic valve (MVG) is measured and used to calculate the AVA using the Gorlin formula: [16]

$$AVA = CO / \left(44.3 * HR * SEP * \sqrt{MVG}\right)$$

where CO (ml/min) is cardiac output, HR (bpm) is heart rate, SEP (sec) is systolic ejection period, and MVG is mean valve gradient.

- The Hakki equation simplified the Gorlin formula for routine use in clinical practice: [17]

$$AVA = CO / \sqrt{MVG}$$

where CO (L/min) is cardiac output and MVG is mean valve gradient.

Additional Testing for LG AS Subtypes

- Distinguishing pseudo severe AS from true severe AS in LF
  - In a LF state, the mean gradient may underestimate the severity of AS as the gradient is highly flow-dependent (true severe AS).
  - In a LF state, the AVA may indicate more severe AS and overestimate the severity due to poor AV leaflet opening due to LF (pseudosevere AS).
- Classical LF-LG AS [18]
  - Dobutamine stress echocardiography (DSE): Low dose (20 μg/kg/min) with goal to increase stroke volume (SV) by >20% to assess changes in mean gradient and AVA with increase in flow. (See Fig. 20-1).
    - Flow reserve (SV increase ≥ 20%)
      - True severe AS: Little or no increase in AVA, increase in mean gradient ≥40 mm hg
      - Pseudosevere AS: increase in AVA, little or no increase in mean gradient.
    - Limited flow reserve (SV increase <20%)
      - Discordant or inconclusive findings on DSE
      - Multidetector computer tomography (MDCT): [19] Hemodynamic independent marker of severity of AS based on calcium scoring.
        - Gender specific cut offs: women ≥1200 AU, men ≥2000 AU
        - Severe AV calcium independently predicts excess mortality after AS diagnosis [20].
- Paradoxical LF-LG AS [18]
  - Assess for factors contributing to reduced SV and LF (i.e. atrial fibrillation, mitral stenosis/regurgitation).
  - Assess for symptoms (consider ETT or exercise echocardiography).
  - If evidence of uncontrolled hypertension (SBP >130 mm Hg), initiate anti-hypertensive regimen prior to reassessment of valve hemodynamics.
  - Evaluate for pseudosevere AS with DSE and/or MDCT as above (see Classic LF-LG AS section) (See Fig. 20-1).
  - Consider cardiac catheterization with nitroprusside challenge to distinguish between moderate and true severe AS.
    - Nitroprusside reduces afterload and LV filling pressures in patients with LG severe AS and preserved EF and may reclassify patients with heightened sensitivity to afterload as having less severe/moderate AS [21].

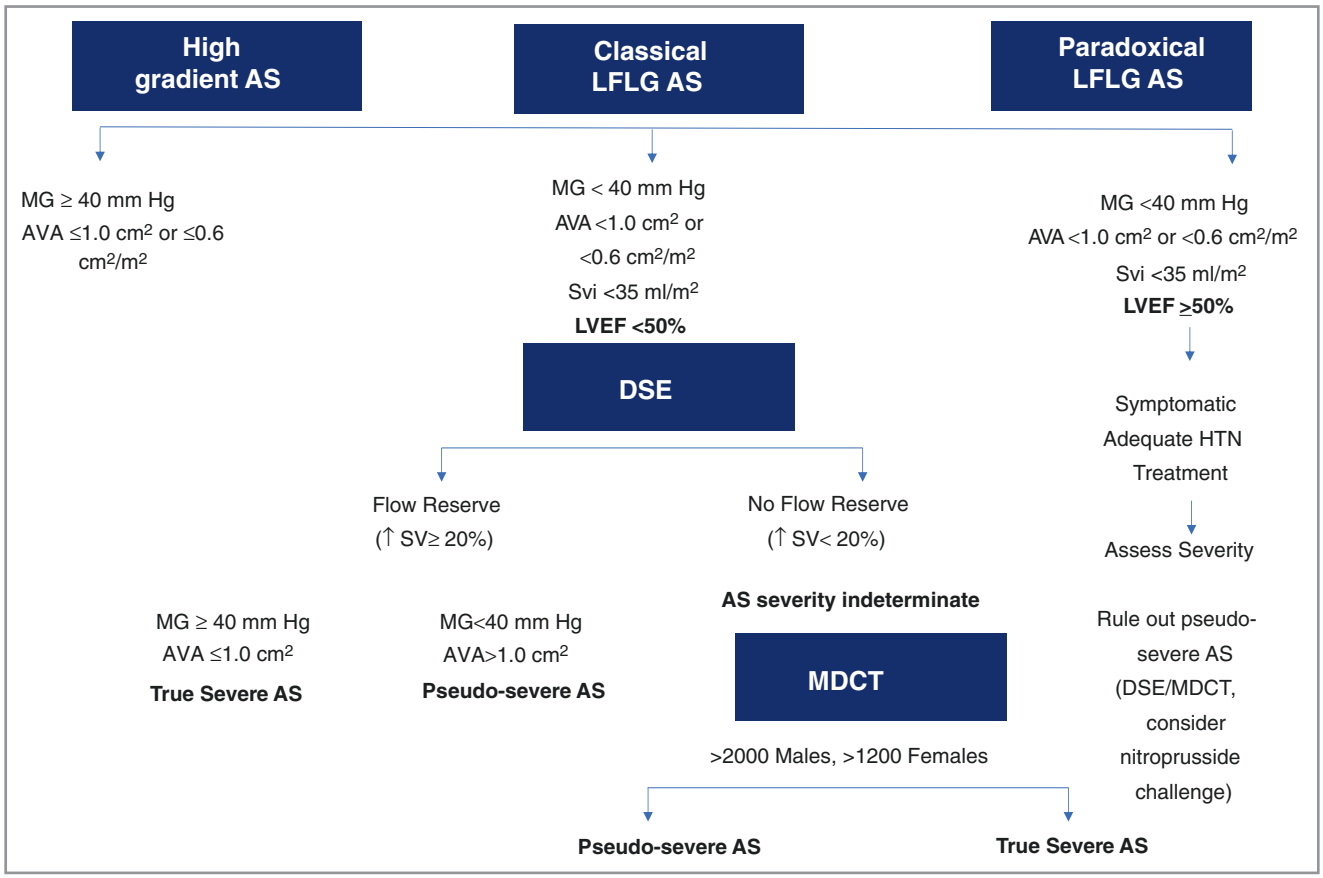

FIGURE 20-1

Algorithm for the Assessment of Stenosis Severity of high gradient, classical LF-LG AS, and paradoxical LF-LG AS. *AS* aortic stenosis, *AVA* aortic valve area, *DSE* Dobutamine stress echocardiography, *HTN* Hypertension, *LFLG* low flow-low gradient, *LVEF* left ventricular ejection fraction, *MDCT* Multidetector computed tomography, *MG* mean gradient, *SV* stroke volume, *SVi* stroke volume index. Adapted from Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. Eur Heart J. 2016; 37(34):2645–57

- NF-LG AS [18]
  - The implications of NF-LG aortic stenosis are unknown.
  - Similar evaluation as above including DSE and/or MDCT to better evaluate the severity of AS.

Natural History

- AS typically progresses slowly over decades (latent phase) with an average rate of progression of 0.1–0.2 cm²/year [22, 23], although more rapid progression is seen with heavily calcified valves [24].
- Aortic sclerosis progresses to severe AS in some, but not all, individuals. Progression from sclerosis to stenosis over a 5-year interval was observed in approximately 9% of the Cardiovascular Health Study (CHS) population, all of who were older than 65 years [25].
- Once symptoms due to severe AS develop, survival worsens.
  - With the development of symptoms (angina, syncope, or heart failure), only 50% of patients will survive at 1 year without surgical intervention [26].
- Sudden death occurs in the setting of severe AS, whether or not symptoms have developed; however, sudden death is rare in asymptomatic AS patients (<1%/year) [15].
- Other complications of AS include LV dysfunction, worsening mitral regurgitation from annular dilation, heart failure, and conduction disease from erosion of calcium at the level

of the aortic annulus into the upper septum and affecting either the atrioventricular node (1st degree block) or the bundles.

- Concomitant ascending aortic dilation is present in patients with bicuspid aortic valves (independent of the degree of stenosis or regurgitation).
  - Dilation of the ascending aorta in a patient with a bicuspid valve is not due to "post-stenotic" turbulence of blood flow; rather it is due to an inherited weakness of the medial smooth muscle integrity.
  - Aortic dissection is a dreaded complication

Management of Severe AS

Pharmacologic

- There are no medical therapies to prevent or slow the progression of AS.
  - While substantial retrospective data suggested that lipid-lowering therapy with statins would slow the progression of AS, randomized clinical trials have not supported this hypothesis [27–29].
  - For patients with dilated ascending aorta, use of beta blockers and possibly vasodilators (such as angiotensin receptor blockers) is recommended to retard progression of dilation and reduce risk for dissection.

Aortic Valve Replacement (AVR)

- The prognosis for severe AS is dismal without AVR upon the development of symptoms and/or depressed LV systolic dysfunction.
- Multiple randomized, multi-controlled trials and registries have now demonstrated both the efficacy and safety of transcatheter aortic valve replacement (TAVR) in patients with severe, symptomatic AS as an alternative for patients at prohibitive, high, and intermediate risk for SAVR [26, 30–32]. The current indications for SAVR/TAVR are listed in Table 20-2.
  - SAVR or TAVR is indicated for survival benefit, improvement in symptoms, and improvement in LV function in patients with symptomatic, severe AS [26].
  - A multidisciplinary heart valve team consisting of interventional cardiology, cardiac imaging, valvular heart disease, and cardiac surgery is recommended for all patients in whom TAVR is considered.

TABLE 20-2

INDICATIONS FOR TYPE OF AORTIC VALVE REPLACEMENT FOR AORTIC STENOSIS

Indications for SAVR	Class
Symptomatic, severe AS and low, intermediate, or high surgical risk	I
Asymptomatic, severe AS and LVEF <50%	I
Severe AS when undergoing other cardiac surgery	I
Asymptomatic, very severe AS (velocity ≥5 m/s) and low surgical risk	IIa
Asymptomatic, severe AS with decreased exercise tolerance or an exercise fall in BP	IIa
Symptomatic, LF-LG severe AS with reduced LVEF with a positive low dose dobutamine stress study (AV ≥4.0 m/s or MG ≥40 mm Hg) with AVA ≤1.0 cm^2 or if LVEF >50% and valve obstruction as the most likely cause of symptoms	IIa
Moderate AS (velocity 3–3.9 m/s) undergoing other cardiac surgery	IIa
Indications for TAVR	
Symptomatic, severe AS and prohibitive risk for SAVR	I
Symptomatic, severe AS and high surgical risk for SAVR	I
Symptomatic, severe AS and intermediate risk for SAVR	IIa

AS aortic stenosis *AVA* aortic valve area, *BP* blood pressure, *EF* ejection fraction, *LF-LF* low flow-low gradient, *LV* left ventricular, *SAVR* surgical aortic valve replacement, *TAVR* transaortic valve replacement. Adapted from [10, 11]

- SAVR is recommended (Class I indication) for symptomatic patients with severe AS.
- SAVR is also recommended in asymptomatic patients with severe AS with depressed LV systolic function (LVEF <50%) (Class I indication).
- Balloon and self-expandable TAVR has demonstrated non-inferiority (all-cause mortality) to SAVR among patients with severe AS at high and intermediate surgical risk [43].
- TAVR is recommended for symptomatic patients with severe AS and a prohibitive risk for SAVR (Class I indication).
- SAVR or TAVR is recommended for symptomatic patients with severe AS at high surgical risk (Class I indication).
- Paradoxical LF-LG AS is a clinically challenging entity to diagnose but is important given its poorer prognosis (compared to normal flow, high gradient AS). Patients with symptomatic LF-LG AS (not pseudosevere AS) benefit from SAVR/TAVR [33].
- In patients with a dilated ascending aorta at the time of surgery, replacement of the aneurysm may be indicated, particularly if the size is >40 mm or if there is a family history of aortic dissection.

Percutaneous Balloon Aortic Valvuloplasty (BAV)

- BAV is a procedure in which a balloon is inflated across the stenotic AV in order to increase valve opening [34].
- BAV is effective for severe AS in children and adolescents; however, its efficacy is limited in adults with calcific AS due to short-lived and only modest clinical benefits.
  - In the current era, BAV is used as a bridge to SAVR/TAVR in unstable patients with severe AS and as a palliative procedure in those in whom other definitive therapies are not feasible [10].

AORTIC REGURGITATION (AR)

Etiology

- Aortic regurgitation (AR) develops due to abnormalities in either the aortic root or the valve leaflets.
  - Acute and chronic AR are distinct clinical entities which will be considered independently.
- There are several causes of chronic AR, the most common of which is dilation of the aortic root and AV annulus. Several other etiologies are also noteworthy (Table 20-3).
- Acute AR is less common and usually due to infective endocarditis, aortic dissection, trauma, or iatrogenic (i.e. post BAV or TAVR).

Pathophysiology and Hemodynamics

- In AR, the fundamental insult is LV volume overload. The extent of overload and regurgitation depends on the regurgitant orifice, the diastolic pressure gradient across the AV, and the duration of diastole.

Chronic AR

- In response to chronic volume overload, eccentric LV hypertrophy develops to accommodate the rise in LV end-diastolic volume. Thus, the compliant LV can accommodate the increased volume load without an increase in end-diastolic pressures.
- Eccentric hypertrophy also results in a larger stroke volume in the setting of preserved LV function; thereby, maintaining effective forward stroke volume.

TABLE 20-3

CAUSES OF AORTIC REGURGITATION

Leaflet abnormalites
Chronic regurgitation
Bicuspid aortic valve
Calcific valve disease
Rheumatic valve disease
Myxomatous valve disease
Rheumatoid arthritis
Nonbacterial thrombotic endocarditis
Systemic lupus erythematosus
Pharmacologic agents
Acute regurgitation
Endocarditis
Iatrogenic leaflet damage
Ruptured leaflet fenestration
Blunt chest trauma
Abnormalities of the aorta
Chronic regurgitation
Marfan syndrome
Bicuspid aortic valve disease
Hypertensive aortic dilation
Familial aortic aneurysm
Cardiovascular syphilis
Ankylosing spondylitis
Other systemic inflammatory disorders
Acute regurgitation
Aortic dissection

- With progressive chronic AR, LV systolic dysfunction ultimately ensues. This further increases LV end-diastolic volume and pressure, resulting in marked LV dilatation and dysfunction.

Acute AR

- With acute AR, there is an acute increase in LV diastolic pressure leading to a drop in forward cardiac output as the LV does not have the time to adapt to the volume load of AR [35].
- Decreased cardiac output is further exacerbated by shortening of the diastolic filling time by compensatory tachycardia and premature closure of the mitral valve.
- Equalization of end-diastolic aortic and left ventricular pressures leads to elevated mean left atrial pressure rises, resulting in pulmonary edema. In severe cases, hemodynamic instability and cardiogenic shock ensue.
- The pre-existence of pressure-overload in which the LV is small and non-compliant results in more dramatic decompensation as these patients possess a steeper diastolic pressure-volume relationship.
- Myocardial perfusion pressure may also diminish as LV end-diastolic pressure approaches the diastolic aortic pressure, resulting in subendocardial ischemia.

Assessment

History

- Until LV end diastolic pressure begins to rise, patients with AR are frequently asymptomatic.
- Symptoms may relate to exaggerated cardiac output with increased stroke volume, including a sense of pounding in the chest.
- Dyspnea is an ominous sign, implying a rise in LV end diastolic pressure with the onset of heart failure.

Physical Examination (See Chap. 1 for Important Details)

- Hallmarks of significant AR include a pulse indicative of both elevated cardiac output and diastolic "run off."
  - Wide pulse pressure (this may normalize in the context of a high LV end diastolic pressure with development of heart failure)
  - Corrigan pulse ("water hammer") characterized by exaggerated upstroke and fall of the arterial pulse, notable in the carotid pulse
- The point of maximal impulse is usually diffuse, hyperdynamic, and displaced laterally and inferiorly in severe chronic AR but may be normal in acute AR.
- The murmur of AR
  - Most often high-pitched ("blowing") in quality but may be harsh when due to aortic leaflet eversion, tearing, or perforation. The intensity of the diastolic murmur does not correlate well with AR severity.
  - A mild AR murmur begins after A2 in early diastole. As regurgitation becomes more severe, the murmur can extend and become holodiastolic. With very severe AR, the murmur may soften or disappear due to near equalization of end-diastolic pressures between the LV and the aorta.
  - The murmur of AR typically radiates along the left sternal border and is best heard with the patient sitting up and leaning forward after full expiration. If the murmur radiates along the right sternal border, it is suggestive of an ectatic aortic root, such as can occur with syphilis or giant cell arteritis.
  - Very significant AR may be accompanied by a low pitched late mitral diastolic rumble (the "Austin-Flint" murmur) due to impingement on the mitral valve by the aortic regurgitant jet.
- Other stigmata of AR are discussed in Chap. 1 but the classical findings of chronic AR (such as head bobbing (de Musset's sign), to-and-fro murmurs over the femoral artery (Duroziez's sign), Quincke's pulse, and higher leg blood pressures compared to arm (Hill's sign) are less evident or absent in acute AR.

Echocardiography

- Echocardiography can be invaluable in identifying the etiology and severity of AR and allows assessment of the ascending aorta.
  - Echocardiography helps to establish the etiology of AR by assessment of leaflet pathology (thickening, calcifications, vegetations, valve morphology) as well as presence of aortic pathology including dilation or dissection.
  - Doppler and color flow echocardiography is used to grade the severity of AR using several parameters (Table 20-4).
    - The ratio of AR jet width/area to LVOT diameter/area correlates with angiographic AR severity.

TABLE 20-4

MEASURES OF AORTIC REGURGITATION SEVERITY

PARAMETER	MILD	MODERATE	SEVERE
Jet width/LVOT	<25%	25%–65%	>65%
Vena contracta (cm)	<0.3	0.3–0.6	>0.6
Pressure half-time (ms)	>500	200–500	<200
Regurgitant volume (mL/beat)	<30	30–60	>60
Regurgitant fraction (%)	<30	30–50	>50
Regurgitant orifice area (cm^2)	<0.10	0.1–0.3	>0.30

LVOT left ventricular outflow tract
Adapted from [10, 11]

- The time required for the AV pressure gradient in diastole to fall by half ("pressure half-time") also correlates with AR severity; however, the ability of this measure to distinguish between grades of AR is limited. Shorter pressure half-times are associated with more severe AR.

– Quantification of the volume and fraction of regurgitant flow is performed by echocardiography as follows:

$$SV_{LVOT} = \left(\text{LVOT diameter}\right)^2 * 0.785 * VTI_{LVOT}$$

$$SV_{MV} = \left(\text{MV annulus diameter}\right)^2 * 0.785 * VTI_{\text{MV inflow}}$$

$$RV = SV_{LVOT} - SV_{MV}$$

$$RF = \left(RV / SV_{LVOT}\right) * 100\%$$

where MV is mitral valve, RF is regurgitant fraction, RV is regurgitant volume, and SV is stroke volume.

- Regurgitant orifice area (ROA) is a robust measure of AR severity that is calculated by dividing the regurgitant volume by regurgitant flow (VTI_{AR}): [36]

$$ROA = RV / VTI_{AR}$$

- Other findings consistent with severe AR include premature closure of the mitral valve, mitral valve fluttering, reversed doming of the anterior mitral valve leaflet, and holodiastolic flow reversal in the descending aorta.
- Over time, chronic AR leads to increased LV end systolic and diastolic volumes with progression to decompensation of LV systolic function.

Cardiac Catheterization

- Invasive assessment of AR severity is recommended when noninvasive tests are inconclusive or discordant with clinical findings.
- Invasive hemodynamic measurements can be helpful in evaluating patients with mixed aortic valve stenosis and regurgitation.
- Supravalvular aortography can be used to grade AR severity based on the degree of contrast regurgitation into the LV (Table 20-5) [38].

TABLE 20-5

SELLER'S CRITERIA FOR GRADING AORTIC REGURGITATION BY ANGIOGRAPHY

GRADE OF REGURGITATION	
1	Small amount contrast enters LV in diastole and is cleared with each beat
2	More contrast fills LV with faint opacification of the entire LV
3	LV is well opacified with contrast density equal to the ascending aorta
4	Complete and dense opacification of the LV on the first beat with contrast density greater than the ascending aorta

LV left ventricle. Adapted from reference [37]

Natural History

- Acute AR is a medical emergency that requires immediate intervention.
- Asymptomatic patients with chronic AR, preserved LV function, and without severe LV dilatation possess a good prognosis.
  - The rate of progression to LV dysfunction and/or symptom development is only 4.3%/year and the rate of sudden death only 0.2%/year.

Management

Pharmacologic

Chronic AR

Pharmacologic therapy in severe AR is limited to symptomatic severe AR or asymptomatic AR with LV systolic dysfunction who are not candidates for AV surgery.

- Vasodilators such as hydralazine, nifedipine and felodipine increase cardiac output and reduce the regurgitant fraction
- Therapy with angiotensin-converting enzyme inhibitors (ACE-I) reduces end-diastolic volume if doses sufficient to reduce systemic blood pressure are administered.
- Long-term therapy with vasodilators is only indicated for those without an indication for valve replacement or in those who cannot undergo surgery.
- Short-term therapy can be instituted for hemodynamic optimization prior to SAVR.

Acute AR

- Medical therapy for acute severe AR should be used solely to maintain hemodynamic stability prior to surgical AVR.
- Intravenous vasodilators, such as nitroprusside, should be used to reduce afterload and LV end-diastolic pressure and to augment cardiac output.
- Inotropic agents can also be used to further increase cardiac output if needed, but are generally not useful.
- To avoid reducing compensatory tachycardia (and avoid prolonging diastole) β-blockers should be avoided, although these agents can be used cautiously in the setting of acute AR due to aortic dissection in order to reduce dP/dT.

Surgical Management of AR

- SAVR is indicated for symptomatic patients with severe AR regardless of LV systolic function. The guidelines for valve replacement surgery in the asymptomatic patient are listed in Table 20-6 [10, 32].
- Surgery is a class I indication for asymptomatic patients with LV dysfunction (LV EF<50%) and those asymptomatic patients with severe AR undergoing concomitant cardiac surgery.

TABLE 20-6

INDICATIONS FOR AORTIC VALVE REPLACEMENT FOR AORTIC REGURGITATION

	CLASS
Symptomatic patients with severe AR regardless of LV systolic function	Class I
Asymptomatic patients with severe AR and LV systolic dysfunction (LVEF <50%)	Class I
Asymptomatic patients with severe AR undergoing cardiac surgery	Class I
Asymptomatic patients with severe AR with normal LV systolic function and severe LV dilatation (LV ESD > 50 mm)	Class IIa
Patients with moderate AR undergoing cardiac surgery	Class IIa
Asymptomatic patients with severe AR and normal LV systolic function (LVEF ≥50%)with severe LV dilatation (EDD > 65 mm) if surgical risk is low	Class IIb

AR aortic regurgitation, *EDD* end diastolic dimension, *EF* ejection fraction, *ESD* end systolic dimension, *LV* left ventricular. Adapted from reference [10, 11]

- SAVR may be considered (Class II) in asymptomatic patients with severe LV dilatation.
- Despite high operative risk, clinical outcomes with SAVR in patients with NYHA class IV symptoms and/or severe LV dysfunction (LV EF ≤25%) are better than with medical therapy alone [39].
- Surgical aortic valve repair (rather than replacement) for AR is feasible, especially in those with bicuspid aortic valves or those with AR due to cusp prolapse.

PULMONIC STENOSIS (PS)

Etiology

- Congenital pulmonic stenosis (PS), the most common etiology, is discussed in this chapter and may be sub-valvular, valvular, or supra-valvular.
- The most common acquired cause of PS is carcinoid disease. PS due to carcinoid often occurs in conjunction with tricuspid valve disease.
- Rheumatic heart disease rarely can lead to fusion of pulmonary valve cusps.
- Functional PS can be due to extrinsic compression of the right ventricular outflow tract by tumor.

Pathophysiology

- PS is characterized by right ventricular (RV) pressure load that leads to RV hypertrophy.
  - RV dysfunction presents in late stages of the disease.

Assessment

History

- Typically asymptomatic. May lead to fatigue and right heart congestive symptoms if severe

Physical Examination (See Chap. 1 for More Details)

- Palpation may reveal an RV heave or a thrill, both are rare.
- Auscultation findings include a harsh systolic murmur that increases with inspiration. The murmur duration increases with the severity of stenosis.
- Associated congenital lesions may be present (i.e. atrial septal defect (ASD) or patent foramen ovale (PFO), with associated right to left shunting with cyanosis.

Echocardiography

- Leaflet fusion (rheumatic)
- Retraction (carcinoid)
- Thickening with systolic doming (congenital)
- Subvalvular/infundibular stenosis (congenital)
- Continuous wave Doppler helps with assessing severity of lesion (peak gradient: mild < 36 mmHg, moderate 36–64 mmHg, and severe > 64 mmHg).

Cardiac Catheterization

- Simultaneous pulmonary artery and RV pressure measurements can confirm pulmonic valve gradient when echocardiography is inconclusive regarding the severity of PS.

Management

- For asymptomatic patients with peak Doppler by echocardiography < 30 mm Hg (mild PS), clinical evaluation and surveillance echocardiography is recommended every five years. For gradients >30 mm Hg, echocardiography is recommended every two to five years [40].
- Therapy for congenital PS is balloon valvuloplasty (discussed in this chapter).
- PS due to carcinoid syndrome may necessitate valve replacement.
- Management of pregnant patients with PS is not discussed in this chapter.

PULMONIC REGURGITATION (PR)

- Mild pulmonic regurgitation (PR) is observed in nearly 80% of healthy adults.

Etiology

- The most common cause of PR is iatrogenic secondary to pulmonary balloon valvuloplasty/surgical valvotomy for Tetralogy of Fallot repair of right ventricular outflow obstruction [40].
- Pulmonary arterial hypertension is the most common cause of secondary PR, followed by infective endocarditis.
- Marfan syndrome can cause pulmonary arterial dilation and concomitant PR.
- Other rare causes of PR include rheumatic heart disease, carcinoid disease, congenital heart disease, and trauma.

Pathophysiology

- PR leads to RV volume overload.
- Early stages of disease are well tolerated unless occurring with significant pulmonary hypertension.
- Late stages of disease are manifested by RV enlargement and dysfunction and functional tricuspid regurgitation.

Assessment

History

- PR is almost always asymptomatic
- Exertional dyspnea and fatigue due to inability of RV to augment cardiac output may develop with progressive RV dysfunction.
- If severe, PR may result in progressive functional tricuspid regurgitation and right sided congestive symptoms (i.e. hepatic congestions, ascites).

Physical Examination (See Chap. 1 for More Details)

- Decrescendo diastolic murmur heard best over the lower left sternal border

Echocardiography Is the Primary Means of Imaging and Grading PR

- 2D imaging can identify valve morphology and motion (doming or prolapse), RV enlargement/hypertrophy, RV function, and pulmonary arterial dilatation.

Cardiac Magnetic Resonance Imaging (MRI) for Quantitative Assessment of Regurgitant Fraction and RV Function Can Aid in the Timing of Intervention on Patients with at Least Moderate PR

Management

- Patients with asymptomatic, severe PR and normal RV function do not require any medical therapy or surgical intervention.
- Surgical or percutaneous pulmonic valve intervention is recommended for patients with symptomatic, severe PR or asymptomatic, severe PR with evidence of RV dysfunction.
  - Severe RV dilation and/or dysfunction is defined as cardiac magnetic resonance (CMR) derived RV end diastolic volume >150 mL/m^2, end systolic volume >80 mL/m^2, EF <47%).
  - Percutaneous pulmonic valve implantation (PPVI) is primarily used to treat severe regurgitation of a pulmonary artery conduits, rarely used for native PR due to variable configuration of the right ventricular outflow tract [41].
    - PPVI has an emerging role in severe PR in the setting of Tetralogy of Fallot post-repair and in failing pulmonic bioprosthetic valves (valve-in-valve).
    - There are no randomized control trials comparing the efficacy and safety of surgical versus percutaneous pulmonic valve replacement. Short and long-term outcomes appear comparable to surgical repair [42].
    - Complications of PPVI include stent fracture, coronary artery compression, and endocarditis.

Questions and Answers

1. A 72-year-old female with history of hypertension and hyperlipidemia has a known history of AS and is referred for cardiovascular consultation for possible surgical intervention. She remains active without any limiting exertional symptoms. Physical exam reveals a heart rate of 65, blood pressure of 117/67 mm Hg, delayed carotid upstrokes bilaterally, a late peaking crescendo murmur heard best at the right upper sternal border with radiation to the carotids. An echocardiogram obtained demonstrates a calcified, tricuspid aortic valve with an aortic valve area of 0.9 cm^2, a mean transvalvular gradient of 42 mm Hg, and preserved left ventricular systolic function (LVEF 60%).

   What is the next best step in the management of this patient?
   a) Exercise stress testing
   b) Referral for surgical AVR
   c) Multidisciplinary heart team meeting for consideration of transcatheter aortic valve replacement (TAVR)
   d) Repeat echocardiogram in 2 years

1. Answer: a. Exercise stress testing. Up to 50% of patients with severe AS report no symptoms at the time of diagnosis. Exercise stress testing can unmask symptoms with exertion or demonstrate an abnormal response to exercise. Patients with asymptomatic, severe AS who develop symptoms on exercise testing (i.e. limiting dyspnea, angina, pre-syncope) have a Class I indication for aortic valve replacement. It is reasonable to also consider aortic valve surgery in patients with an abnormal response to exercise testing including a drop in blood pressure and/or decreased exercise tolerance (Class IIb). Patients with asymptomatic, severe AS with pre-

served LV systolic function and no other indication for cardiac surgery are not candidates for aortic valve surgery. Transcatheter aortic valve replacement (TAVR) is only recommended for patients with symptomatic severe AS at prohibitive to high surgical risk for surgical AVR (Class I) and considered for patients at intermediate surgical risk (Class IIa). Patients with severe, asymptomatic AS should be followed clinically with echocardiography every 6–12 months (Class I).

2. A 64-year-old male with no known cardiovascular history is referred for cardiac consultation for a heart murmur. The patient has remained active without cardiovascular symptoms. Physical examination reveals a blood pressure of 105/40 mmHg and an exaggerated carotid upstroke. In addition, a II/VI, blowing, diastolic murmur is heard along the right sternal border and a II/VI diastolic rumble is noted at the apex. An echocardiogram is obtained demonstrating severe aortic regurgitation, a left ventricular ejection fraction of 55%, and left ventricular end systolic dimension of 57 mm.

   What is the best next step in the management of this patient?
   a) Initiation of an angiotensin-converting enzyme inhibitor
   b) Percutaneous mitral balloon valvuloplasty
   c) Surgical aortic valve replacement
   d) Exercise echocardiography
   e) Hospital admission for nitroprusside infusion

   2. Answer: c. Surgical aortic valve replacement. Asymptomatic severe aortic regurgitation is an indication for surgical aortic valve replacement in the presence of left ventricular dysfunction (ejection fraction ≤50%; Class I) or severe dilatation (end diastolic dimension >65 mm or end systolic dimension >50 mm). Vasodilators are the mainstay of therapy for asymptomatic severe aortic regurgitation if there is evidence of LV systolic dysfunction who are not candidates for AV surgery. They may also be used for hemodynamic optimization prior to surgery, but the patient presented here has no evidence of heart failure and has a relatively low blood pressure. While the patient has a diastolic murmur in the mitral position ("Austin-Flint" murmur), indicative of severe AR, the mitral valve is morphologically normal without mitral stenosis on echocardiography. Exercise testing is reasonable in patients with severe AR for assessment of functional status and symptoms, although the role of observed changes in left ventricular function with exercise are unclear. Poor exercise tolerance in an "asymptomatic" patient with normal left ventricular size and function may be used to justify aortic valve replacement in the absence of other clear reason if surgical risk is low. Nitroprusside infusion is useful for afterload reduction in patients with severe acute aortic regurgitation.

3. A patient with aortic stenosis presents for evaluation. Echocardiographic findings include LVOT diameter 2.0 cm; LVOT VTI 25 cm; AV peak velocity 4.76 m/sec; mean transvalvular gradient 64 mmHg; AV VTI 131 cm; body surface area (BSA) 1.90 sqcm. Which of the following is the effective orifice area (EOA) of the aortic valve.
   a) EOA is 0.8 cm^2; EOA index 0.4 cm^2/m^2
   b) EOA is 0.6 cm^2; EOA index 0.3 cm^2/m^2
   c) EOA is 0.8 cm^2; EOA index 1.5 cm^2/m^2
   d) EOA is 0.6 cm^2; EOA index 1.1 cm^2/m^2

   3. Answer: b. The effective orifice area is equal to $(CSA_{LVOT} \times VTI_{PVOT})/VTI_{AV}$. The CSA_{LVOT} equals πr_{lvot}^2. The LVOT diameter is 2.0 cm, therefore the LVOT radius is 1.0 cm. The CSA_{LVOT} equals $\pi 1^2$, or 3.14 cm^2. The EOA of the aortic valve is $(3.14 \times 25)/131 = 0.59$ cm^2. The EOA index is the EOA/BSA = 0.59/1/90 = 0.31.

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CHAPTER 21

MAYOORAN NAMASIVAYAM, RICARDO J. CIGARROA, IGNACIO INGLESSIS, AND JUDY W. HUNG

Mitral and Tricuspid Valve Disease

CHAPTER OUTLINE

ABBREVIATIONS

ACC	American College of Cardiology
AF	Atrial fibrillation
AVR	Aortic valve replacement
AHA	American Heart Association
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CMR	Cardiovascular magnetic resonance (imaging)
CRT	Cardiac resynchronization therapy
CT	Computed tomography
DOAC	Direct oral anticoagulant
DT	Deceleration time
EROA	Effective regurgitant orifice area
GDMT	Goal directed medical therapy
HF	Heart failure
LA	Left atrium/atrial
LV	Left ventricle/ventricular
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic dimension
LVOT	Left ventricular outflow tract
MR	Mitral regurgitation
MS	Mitral stenosis
MV	Mitral valve
MVA	Mitral valve area
MVP	Mitral valve prolapse
MVR	Mitral valve replacement
NYHA	New York Heart Association
PASP	Pulmonary artery systolic pressure
PHT	Pressure half time
PISA	Proximal isovelocity hemispheric surface area
PMBC	Percutaneous mitral balloon commissurotomy
RA	Right atrium/atrial
RV	Right ventricle/ventricular
TEE	Transesophageal echocardiography
TR	Tricuspid regurgitation

TS	Tricuspid stenosis
TV	Tricuspid valve
TTE	Transthoracic echocardiography
VKA	Vitamin K antagonist
VTI	Velocity time integral

INTRODUCTION

- Atrioventricular valve dysfunction can lead to significant alterations in cardiovascular physiology, morbidity and mortality
- This chapter will outline the key concepts related to mitral and tricuspid valve disease, with particular reference to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines
  - Guidelines referenced are those of 2014 and the focused update of the 2014 guidelines published in 2017
    - We urge the reader to check for subsequent AHA/ACC updates to the guidelines which occur after publication of this book

MITRAL VALVE DISEASE

Mitral Valve Anatomy

- Complex 3D, non-planar structure
- Anterior and posterior leaflets
  - Anterior leaflet is longer and narrower than the posterior leaflet
  - Each leaflet comprised of 3 scallops—numbered 1–3 from lateral to medial
- Chordae tendineae
  - Primary
    - Insert to free margin of leaflets
  - Secondary
    - Insert to corrugated surface of leaflets
  - Tertiary
    - Insert to basal aspect of posterior leaflet
- Papillary muscles
  - Anterolateral
    - Supplied by the diagonal branches of the left anterior descending coronary artery and obtuse marginal of the left circumflex coronary artery
  - Posteromedial
    - Usually single vessel supply from posterior descending coronary artery
      - Single vessel supply—more likely to be compromised by infarction, thus more likely to have infarction-mediated transection of papillary muscle heads

Mitral Stenosis

Etiology

- Mitral stenosis (MS) can be due to:
  - Rheumatic disease
  - Senile calcific disease
  - Miscellaneous causes
    - congenital
      - parachute mitral valve (MV)
      - cor triatriatum
      - double orifice MV
      - supravalvular mitral ring
    - systemic inflammatory disorders
      - systemic lupus erythematosus
      - rheumatoid arthritis
    - lysosomal storage disorders
    - radiation valvulitis
      - typically manifests 10–20 years following mediastinal radiation exposure
    - obstructive lesions ("functional MS")
      - tumor (atrial myxoma)
      - infective vegetation

Physiology

- As MS worsens, a pressure gradient develops between the left atrium (LA) and left ventricle (LV) during diastole
  - LA pressure rises
    - Atrial dilation
      - Atrial fibrillation (AF)
    - Increased pulmonary arterial pressures
      - Pulmonary edema
      - Pulmonary hypertension
        - Can lead to right ventricular dysfunction and tricuspid regurgitation
  - Antegrade flow falls
    - Low cardiac output
  - LA pressure rise and anterograde flow reduction worsened by tachycardia due to shortened diastolic duration
    - Less LV filling time, therefore higher flow rate required to maintain flow, resulting in higher gradient; this is known as the "mitral block" phenomenon.

Clinical Assessment

- History
  - The symptoms of MS typically relate to degree of obstruction and elevation of left atrial pressure, and include:
    - Dyspnea, orthopnea, and paroxysmal nocturnal dyspnea
    - Palpitations (if atrial fibrillation develops)
    - Chest discomfort
    - Hemoptysis
    - Peripheral or cerebral embolization
    - Fatigue
  - Ortner's syndrome- in advanced mitral stenosis, hoarseness may occur due to vocal cord paralysis from impingement of the left recurrent laryngeal nerve by an enlarged left atrium
  - Importantly, *all of these symptoms may acutely worsen during pregnancy*, to the point of cardiogenic shock.
- Physical examination (see Chap. 1 for further details)
  - On palpation, the apex of the heart is typically non-displaced but if pulmonary hypertension has developed then a *right ventricular heave* may be present
  - Auscultation of the heart in MS is best achieved with the patient in the *left lateral decubitus position*, and has several important hallmarks, including:
    - Loud S1 opening snap
    - Mid-diastolic rumbling murmur, which may have pre-systolic accentuation if the patient is in sinus rhythm
  - In advanced cases, signs and symptoms of pulmonary congestion, pulmonary hypertension, and right heart failure may be present.
  - Atrial fibrillation is commonly present.
  - In advanced mitral stenosis patients may develop "mitral facies", rosy cheeks with a bluish tinge (also referred to as plum-colored malar rash), due to cyanosis from low cardiac output and cutaneous vasodilation.

Echocardiographic Features of Rheumatic MS

- Anterior leaflet doming ('hockey stick' appearance)
- Posterior leaflet immobility
- Chordal thickening
  - Can also see chordal shortening and chordal fusion
- Commissural fusion—'fish mouth' appearance of MV in short axis view
  - Main mechanism of rheumatic MS is fusion of the commissures and subvalvular apparatus

Quantification of MS

- Mean diastolic pressure gradient
  - Flow dependent (and hence heart rate dependent)
    - Not part of the AHA/ACC criteria for management of AS in 2014 or 2017 update, but is to be considered for calcific, non-rheumatic MS, where other quantitative measures are not to be used (e.g. pressure half time)

- Gradient classification:
  - <5 mmHg mean gradient, mild
  - 5–10 mmHg mean gradient, moderate
  - >10 mmHg mean gradient, severe

- MV area
  - Can be calculated by a variety of methods
    - Planimetry
      - 2D or 3D echocardiographic planimetry
    - Pressure half time (PHT) (Fig. 21-1)
      - The time taken for maximal early diastolic gradient to fall to half
      - MV area (cm^2) = 220/PHT (ms)
    - Deceleration time (DT) (Fig. 21-1)
      - The time for maximal early diastolic gradient to fall to zero
      - MV area (cm^2) = 759/DT (ms)
    - Continuity equation
      - MV area = [LVOT area × LVOT VTI]/MV VTI
        - Where LVOT is left ventricular outflow tract, MV is mitral valve and VTI is velocity time integral
    - Proximal isovelocity surface area (PISA) method
      - MV area = $2 \times \Pi \times r^2 \times [V_{alias}/V_{max}] \times [\Theta/180]$

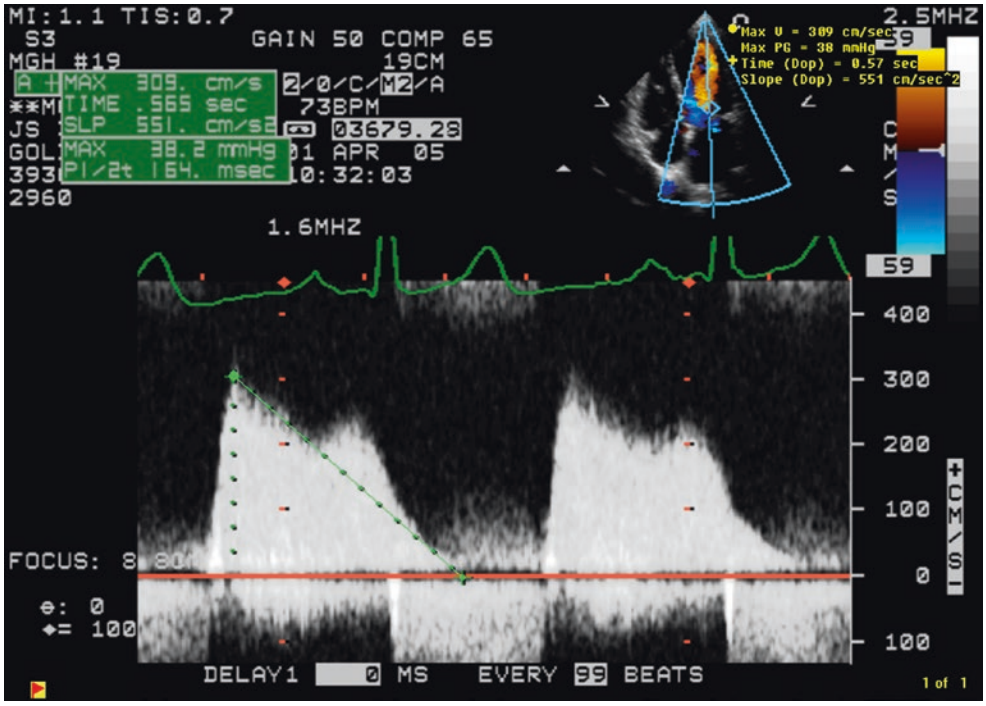

FIGURE 21-1

Measurement of time taken for maximal early diastolic gradient to fall to half is pressure half time, whilst time taken to fall to zero is deceleration time. The longer the times, the more severe the MS. Note that whilst pressure half time is useful in rheumatic MS, it should not be used as a marker of severity in senile, calcific MS

- Where,
  - r is PISA radius
  - V_{alias} is aliasing velocity
  - V_{max} is maximal transmitral velocity
  - Θ is angle between 2 mitral leaflets in diastole

- Gorlin equation
  - MV area = [cardiac output/(systolic ejection time × heart rate × 44.3 × $\sqrt{}$mean gradient)]

Severe vs. very severe MS (note that pressure half time not recommended in senile, calcific MS—use gradients instead)

- Severe MS
  - MVA ≤ 1.5 cm^2
  - PHT ≥ 150 ms
- Very severe MS
  - MVA ≤ 1.0 cm^2
  - PHT ≥ 220 ms
- Secondary changes resultant from MS visible on echocardiography
  - LA dilation
  - Pulmonary hypertension
  - Right ventricular (RV)/right atrial (RA) dilation
  - Functional tricuspid regurgitation (TR)

Classification of Rheumatic MS

- Rheumatic heart disease
  - Mechanism is an exaggerated immune response resulting in cross-reactivity between valve tissue and streptococcal antigen
  - Rheumatic MV shown in Fig. 21-2.

The classification of rheumatic MS is based on valvular anatomy, hemodynamics and symptoms.

- summarized in Table 21-1

Diagnosis and Follow-up

- Class I
  - Transthoracic echocardiography (TTE) is indicated in patients with signs or symptoms of MS to establish the diagnosis, quantify hemodynamic severity (mean pressure gradient, mitral valve area and pulmonary artery pressure), assess concomitant valvular lesions and demonstrate valve morphology (in order to determine suitability for mitral commissurotomy) (Level of Evidence: B)
  - Transesophageal echocardiography (TEE) should be performed in patients considered for percutaneous mitral balloon commissurotomy to assess the presence or of left atrial thrombus and to further evaluate the severity of mitral regurgitation (MR) (Level of Evidence: B)
  - Exercise testing with Doppler or invasive hemodynamic assessment is recommended to evaluate the response of the mean mitral gradient and pulmonary artery pressure in patients with MS when there is a discrepancy between the resting Doppler echocardiographic findings and clinical symptoms or signs (Level of Evidence: C)

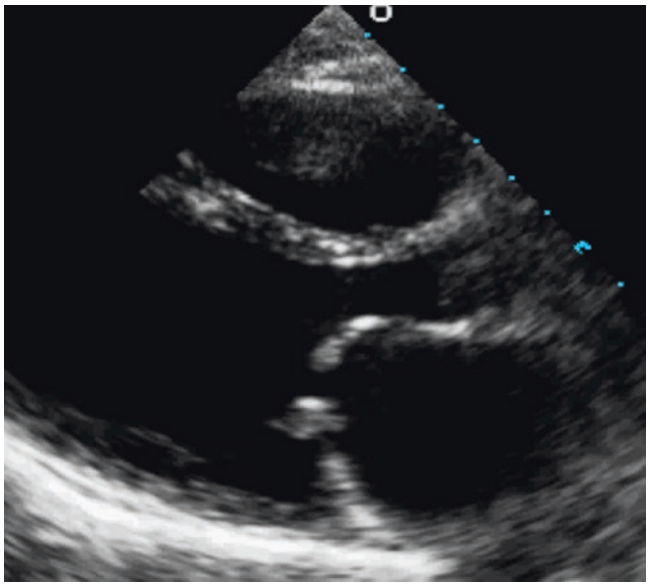

FIGURE 21-2

Rheumatic MS showing thickened, restricted posterior leaflet, and doming of the anterior leaflet with characteristic 'hockey stick' appearance

TABLE 21-1

CLASSIFICATION OF MS

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	At risk of MS	Mild valve doming during diastole	Normal transmitral flow velocity	None	None
B	Progressive MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA > 1.5 cm^2	Increased transmitral flow velocities MVA >1.5 cm^2 Diastolic PHT <150 ms	Mild-to-moderate LA enlargement Normal pulmonary pressures at rest	None
C	Asymptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS)	MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS) Diastolic PHT ≥150 ms (Diastolic PHT ≥220 ms with very severe MS)	Severe LA enlargement Elevated PASP >30 mmHg	None
D	Symptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS)	MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS) Diastolic PHT ≥150 ms (Diastolic PHT ≥220 ms with very severe MS)	Severe LA enlargement Elevated PASP >30 mmHg	Decreased exercise tolerance Exertional dyspnea

Source: Nishimura et al. J Am Coll Cardiol. 2014;63:e57–e185

Management of Rheumatic MS

- Management consists of medical therapy and interventions (percutaneous vs. surgery)

Medical Therapy

- Class I:
  - Anticoagulation (vitamin K antagonist [VKA] or heparin) is indicated in patients with 1) MS and AF (paroxysmal, persistent, or permanent), 2) MS and a prior embolic event, or 3) MS and a left atrial thrombus (Level of Evidence: B)
    - Note that direct oral anticoagulants (DOACs) are not to be used in AF in the presence of MS
- Class IIa
  - Heart rate control can be beneficial in patients with MS and AF and fast ventricular response (Level of Evidence: C)
- Class IIb
  - Heart rate control may be considered for patients with MS in normal sinus rhythm and symptoms associated with exercise (Level of Evidence: B)

Interventions

- Suitability for percutaneous intervention depends on valve morphology, presence of left atrial appendage thrombus (contraindication) and degree of concomitant MR
- Class I
  - Percutaneous mitral balloon commissurotomy (PMBC) is recommended for ***symptomatic*** patients with severe MS (mitral valve area ≤1.5 cm^2, stage D) and favorable valve morphology in the absence of left atrial thrombus or moderate-to-severe MR (Level of Evidence: A)
  - Mitral valve surgery (repair, commissurotomy, or valve replacement) is indicated in ***severely symptomatic*** patients (NYHA class III to IV) with severe MS (mitral valve area ≤1.5 cm^2, stage D) who are not high risk for surgery and who are not candidates for or who have failed previous PMBC (Level of Evidence: B)
  - Concomitant mitral valve surgery is indicated for patients with severe MS (mitral valve area ≤1.5 cm^2, stage C or D) undergoing cardiac surgery for other indications (Level of Evidence: C)
- Class IIa
  - PMBC is reasonable for asymptomatic patients with very severe MS (MV area ≤1.0 cm^2, stage C) and favorable valve morphology in the absence of left atrial thrombus or moderate-to-severe MR (Level of Evidence: C)
  - MV surgery is reasonable for severely symptomatic patients (NYHA class III to IV) with severe MS (MVA ≤1.5 cm^2, stage D), provided there are other operative indications (e.g. aortic valve disease, coronary artery disease (CAD), aortic aneurysm) (Level of Evidence: C)
- Class IIb
  - PMBC may be considered for asymptomatic patients with severe MS (MV area ≤1.5 cm^2, stage C) and valve morphology favorable for PMBC in the absence of left atrial thrombus or moderate-to-severe MR who have new onset of AF (Level of Evidence: C)

- PMBC may be considered for symptomatic patients with MV area >1.5 cm^2 if there is evidence of hemodynamically significant MS based on pulmonary artery wedge pressure >25 mmHg or mean MV gradient >15 mmHg during exercise (Level of Evidence: C)
- PMBC may be considered for severely symptomatic patients (NYHA class III to IV) with severe MS (MV area ≤1.5 cm^2, stage D) who have a suboptimal valve anatomy and who are not candidates for surgery or are at high risk for surgery (Level of Evidence: C)
- Concomitant MV surgery may be considered for patients with moderate MS (MVA 1.6–2.0 cm^2) undergoing cardiac surgery for other indications (Level of Evidence: C)
- MV surgery and excision of the left atrial appendange may be considered for patients with severe MS (MV area ≤1.5 cm^2, stages C and D) who have had recurrent embolic events while receiving adequate anticoagulation (Level of Evidence: C)

■ Determining interventions in MS

- Fig. 21-3

■ Determining suitability for percutaneous mitral balloon commissurotomy (PMBC) based on valve morphology

- Table 21-2

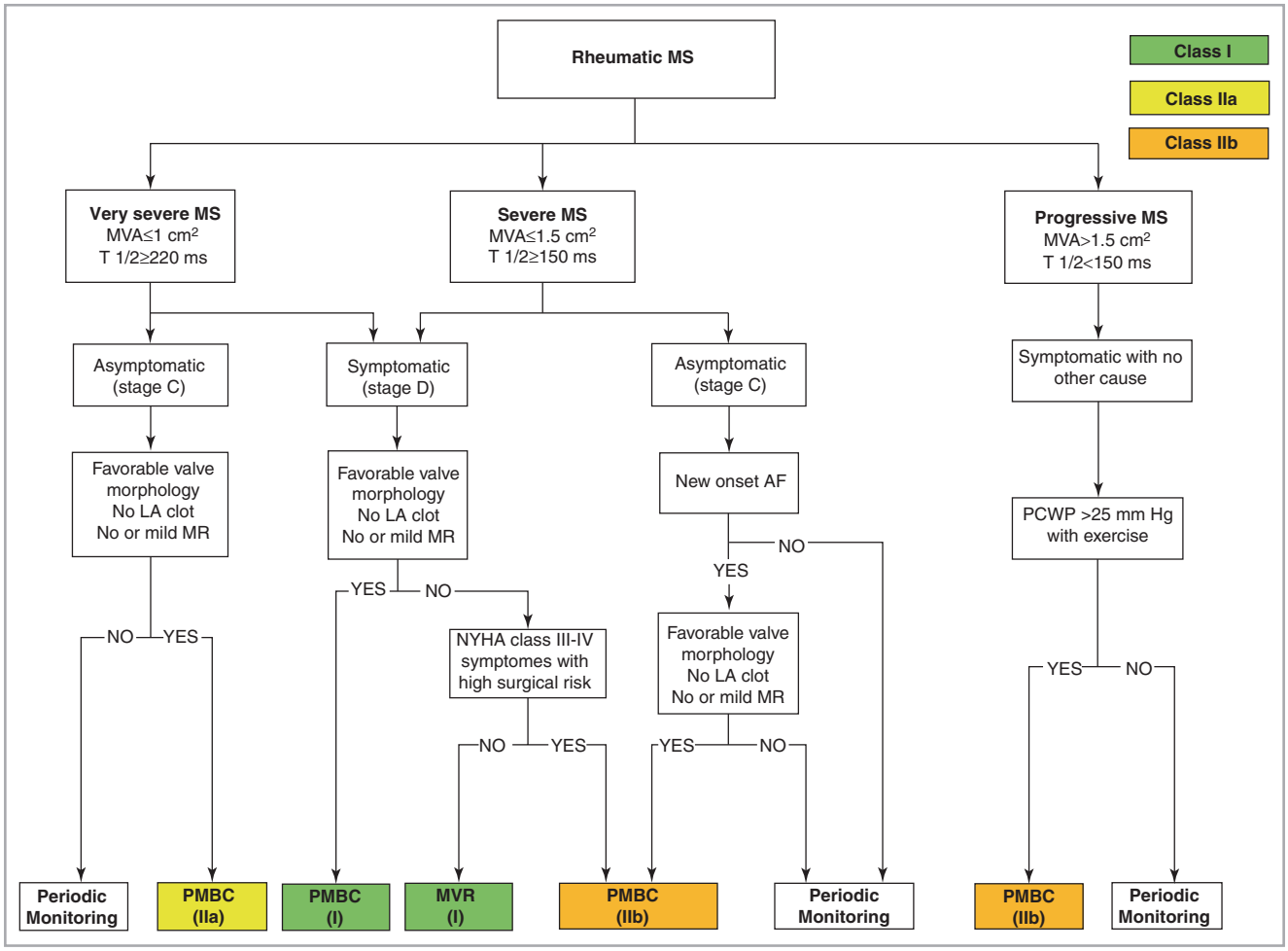

FIGURE 21-3

Indications for intervention for rheumatic MS. *AF* indicates atrial fibrillation, *LA* left atrial, *MR* mitral regurgitation, *MS* mitral stenosis, *MVA* mitral valve area, *MVR* mitral valve surgery (repair or replacement), *NYHA* New York Heart Association, *PCWP* pulmonary capillary wedge pressure, *PMBC* percutaneous mitral balloon commissurotomy; and T ½, pressure half-time. Source: Nishimura et al. J Am Coll Cardiol. 2014;63:e57–e185

TABLE 21-2

ECHOCARDIOGRAPHIC SCORING OF SUITABILITY FOR PMBC IN MS

GRADE	MOBILITY	SUBVALVULAR THICKENING	THICKENING	CALCIFICATION
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness
2	Leaflet mild and base portions have normal mobility	Thickening of chordal structures extending upto one third of the chordal length	Mid-leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid-portion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue

Source: Wilkins et al. Br Heart J. 1988;60:299–308

Calcific (Senile) MS

- Pathophysiology
  - Annular calcification which extends into leaflets (Fig. 21-4)
- Classification
  - Based on gradient criteria
    - <5 mmHg mean gradient, mild
    - 5–10 mmHg mean gradient, moderate
    - >10 mmHg mean gradient, severe
  - PHT measurement is **not recommended** for severity assessment in calcific, non-rheumatic MS (use gradient classification above)
- Management guidelines refer to ***medical therapy only***
  - Same medical therapy guidelines as used for rheumatic MS
  - **No recommendations** for PMBC or surgery

Mitral Regurgitation

Clinical Assessment

- History
  - The symptoms associated with MR depend on the phase of disease
    - In acute severe MR, the patient typically has hallmark symptoms of acutely decompensated heart failure
    - In chronic compensated MR, symptoms may be entirely absent
    - In chronic decompensated MR, symptoms may be very subtle and relate to decreased exercise tolerance and volume sensitivity.

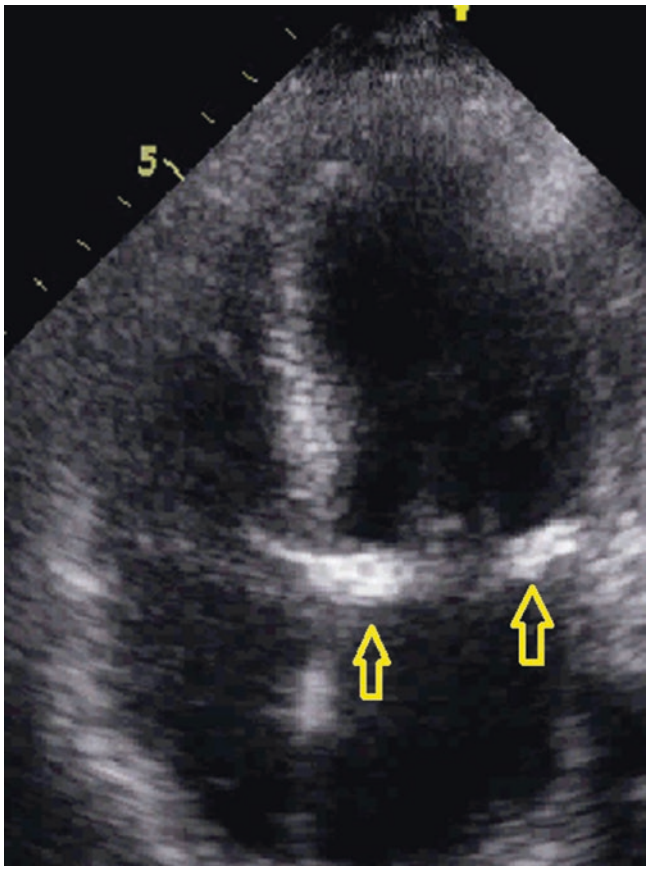

Figure 21-4

Calcific MS. Note significant annular calcification (arrows)

- Physical examination (see Chap. 1 for more details)
  - Findings on physical examination associated with MR depend on the phase of the disease
    - In acute severe MR, the apical impulse is usually normal in location and hyperdynamic.
    - The murmur or acute severe MR may be quite subtle if "wide open" regurgitation is present (such as due to transection of a papillary muscle head), but when due to rupture of a chordae, the murmur is typically quite harsh.
    - In chronic forms of MR, the apical impulse may be displaced. Auscultation reveals a relatively soft first heart sound, followed by a holosystolic blowing murmur.
    - In patients with chronic MR due to MVP, a mid-systolic click may be appreciated, but as the degree of MR progresses, this may be lost.
    - Radiation of the MR murmur is dependent on the vector of regurgitation.
      - For central MR, the murmur is typically heard to radiate to the back or clavicular area
      - For eccentric MR (such as which occurs in those with asymmetric leaflet pathology, including MVP), the murmur radiates differentially: anterior leaflet pathology results in radiation to the axilla, while posterior leaflet pathology results in radiation to the base, sometimes masquerading as AS.
    - An S3 gallop is typically present in advanced MR
- Classified into primary or secondary MR
  - These entities can co-exist

Primary MR

- Pathology in one or more valve components
  - Leaflets
  - Chordae tendinae
  - Papillary muscle
  - Annulus (different to annular dilation caused by ventricular dilation in secondary MR)
- Mitral valve prolapse (MVP) (commonest cause of primary MR) (Fig. 21-5)
  - Spectrum of pathophysiology with 2 entities at the extreme
    - Barlow's disease
      - Myxomatous degeneration
        - Mucopolysaccharide accumulation
      - Fibroelastic deficiency
      - Connective tissue abnormality
        - Loss of mechanical integrity
  - Systolic displacement of one or both mitral leaflets of ≥ 2 mm beyond the annular plane
  - Occurs with or without MR

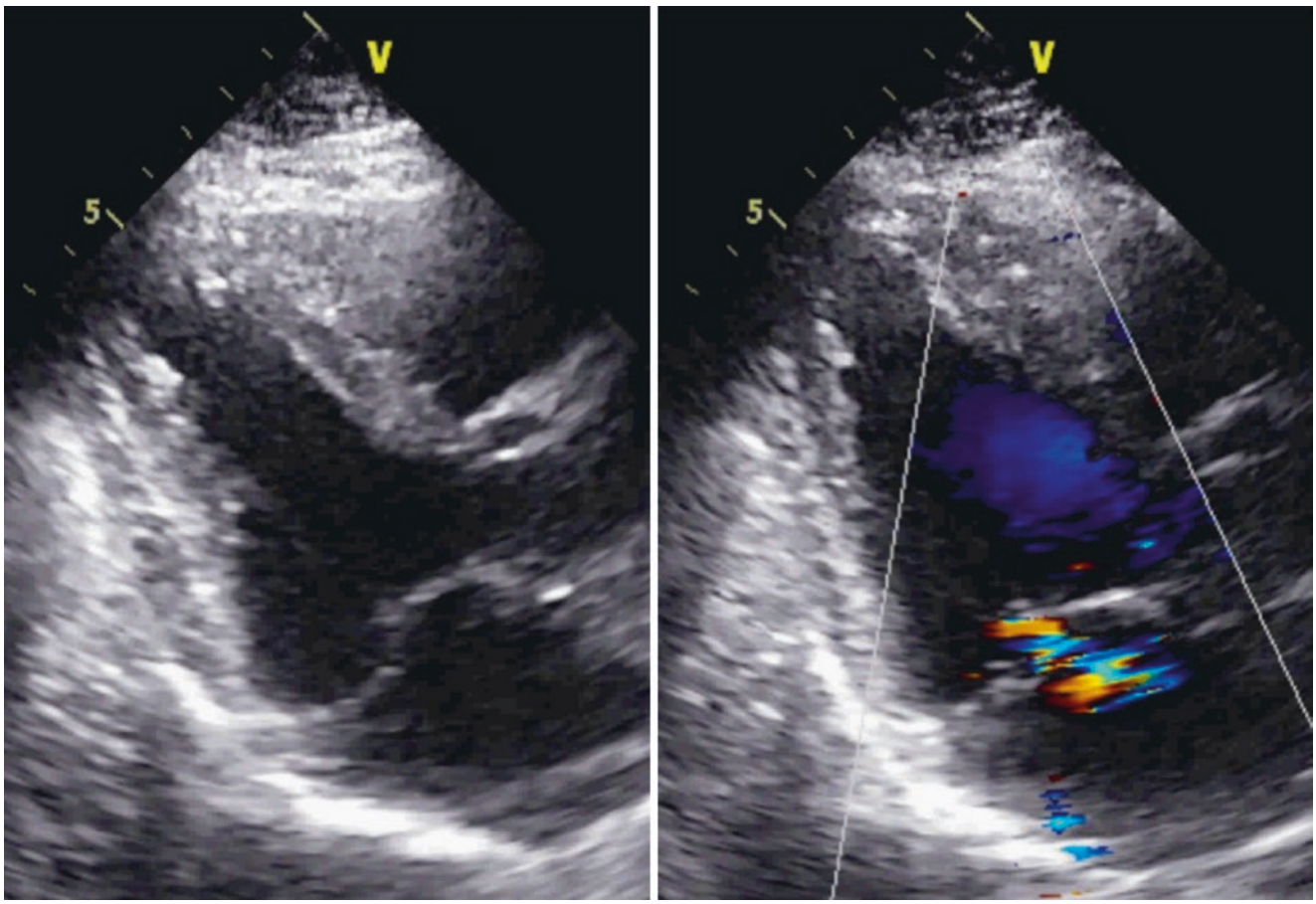

FIGURE 21-5

Posterior mitral valve leaflet prolapse resulting in MR

- Occurs with or without leaflet thickening
  - In those with leaflet thickening, myxomatous change is present on pathoanatomy
- Flail leaflet (Fig. 21-6)
  - Tip of leaflet prolapses into the LA due to loss of convex shape of mitral leaflet
  - Always associated with significant MR even if jet is not obvious on echo images (typically due to an eccentric MR jet)

- Other causes of primary MR
  - Infective endocarditis
  - Rheumatic heart disease
  - Cleft mitral valve
  - Radiation heart disease

Stages of Primary MR

- Table 21-3

Diagnosis and Follow-up

- Class I
  - TTE is indicated for baseline evaluation of LV size and function, RV function and left atrial size, pulmonary artery pressure and mechanism and severity of primary MR (stages A to D) in any patient suspected of having primary MR (Level of Evidence: B)
  - Cardiovascular magnetic resonance imaging (CMR) is indicated in patients with chronic primary MR to assess LV and RV volumes, function or MR severity when these issues are not satisfactorily addressed by TTE (Level of Evidence: B)

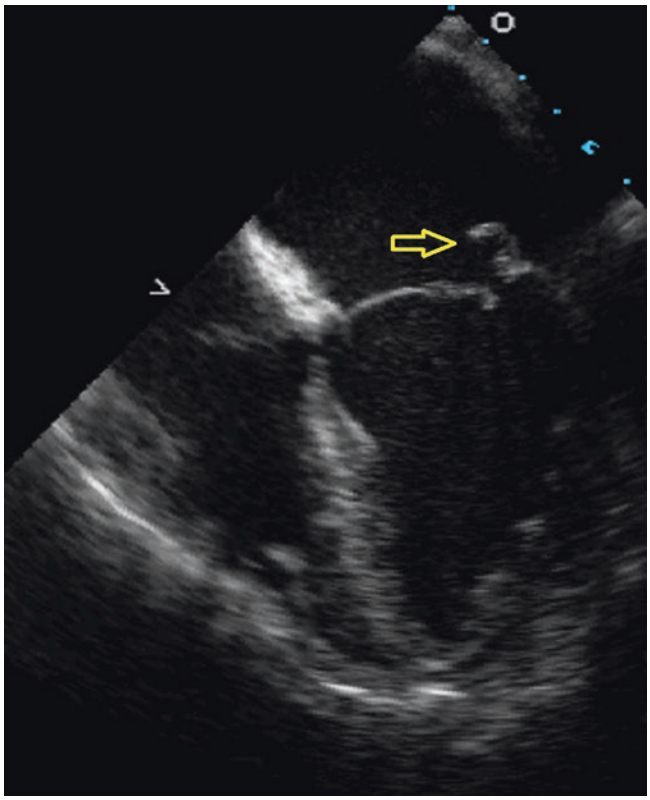

Figure 21-6

Flail posterior leaflet (arrowed). Note protrusion into the LA and loss of convex shape

TABLE 21-3

STAGES OF PRIMARY MR

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	At risk of MR	Mild MV prolapse with normal coaptation Mild valve thickening and leaflet restriction	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.3 cm	None	None
B	Progressive MR	Severe MV prolapse with normal coaptation Rheumatic valve changes with leaflet restriction and loss of coaptation Prior IE	Central jet MR 20%–40% LA or late systolic eccentric jet MR Vena contracta <0.7 cm Regurgitant volume <60 mL Regurgitant fraction <50% ERO <0.4 cm^2 Angiographic grade 1–2+	Mild LA enlargement No LV enlargement Normal pulmonary pressure	None
C	Asymptomatic severe MR	Severe MV prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 mL Regurgitant fraction ≥50% ERO ≥0.4 cm^2 Angiographic grade 3–4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension may be present at rest or with exercise C1: LVEF >60% and LVESD <40 mm C2: LVEF ≤60% and LVESD ≥40 mm	None
D	Symptomatic severe MR	Severe MV prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 mL Regurgitant fraction ≥50% ERO ≥0.4 cm^2 Angiographic grade 3–4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension present	Decreased exercise tolerance Exertional dyspnea

Source: Nishimura et al. J Am Coll Cardiol. 2014;63:e57–e185

- Intraoperative TEE is indicated to establish the anatomic basis for chronic primary MR (stages C and D) and to guide repair (Level of Evidence: B)
- TEE is indicated for evaluation of patients with chronic primary MR (stages B to D) in whom non-invasive imaging provides nondiagnostic information about severity of MR, mechanism of MR, and/or status of LV function (Level of Evidence: C)

■ Class IIa

- Exercise hemodynamics with either Doppler echocardiography or cardiac catheterization is reasonable in symptomatic patients with chronic primary MR where there is a discrepancy between symptoms and the severity of MR at rest (stages B and C) (Level of Evidence: B)
- Exercise treadmill testing can be useful in patients with chronic primary MR to establish symptom status and exercise tolerance (stages B and C) (Level of Evidence: C)

Quantitative Assessment of MR

■ Proximal isovelocity hemispheric surface area (PISA)

- More accurate for central than eccentric jets
- More accurate for circular orifice than non-circular orifice
- Better in primary rather than secondary MR

■ Uses aliasing velocity at radial distance to calculate volume flow rate (VFR)
■ EROA (effective regurgitant orifice area) = VFR/Vmax
■ Regurgitant volume = EROA × MR VTI (velocity time integral)

Cutoffs for Severe Primary (or Secondary) MR

■ EROA $\geq 0.4\ cm^2$
■ Regurgitant fraction $\geq 50\%$
■ Regurgitant volume ≥ 60 mL

Management of Primary MR

Medical Therapy

■ Class IIa:

- Medical therapy for systolic dysfunction is reasonable in symptomatic patients with chronic primary MR (stage D) and left ventricular ejection fraction (LVEF) <60% in whom surgery is not contemplated (Level of Evidence: B)

■ Class III: no benefit

- Vasodilator therapy is **not indicated** for normotensive asymptomatic patients with chronic primary MR (stages B and C1) and normal LV systolic function (Level of Evidence: B)

Surgical Intervention for Primary MR

■ Class I

- Symptomatic severe MR and LVEF >30% (Level of Evidence: B)
- Asymptomatic but LVEF 30–60% and/or left ventricular end-systolic dimension (LVESD) >40 mm (stage C2) (Level of Evidence: B)

- If posterior leaflet only
  - MV repair preferred (Level of Evidence: B)
- If anterior or both leaflets
  - MV repair still preferred over MV replacement if successful and durable repair can be accomplished (Level of Evidence: B)
- Concomitant MV repair or MVR indicated for patients with chronic ***severe*** MR undergoing other cardiac surgery (Level of Evidence: B)

- Class IIa
  - Asymptomatic chronic severe MR with preserved LV function (LVEF >60%; LVESD <40 mm; stage C1) with 95% chance of successful and durable repair, with an expected mortality <1%, when performed at a Heart Valve Center of Excellence (Level of Evidence: B)
  - Asymptomatic chronic severe MR with LVEF>60% and LVESD <40 mm (stage C1), with progressive increase in LV size or decrease in EF on serial imaging studies (Level of Evidence: C)
  - Asymptomatic chronic severe nonrheumatic MR with preserved LV function (LVEF >60%; LVESD <40 mm; stage C1) and:
    - new onset atrial fibrillation (AF) (Level of Evidence: B)
    - resting pulmonary hypertension (pulmonary artery systolic pressure >50 mmHg) (Level of Evidence: B)
  - Concomitant MV repair is reasonable in patients with chronic ***moderate*** primary MR (stage B) undergoing other cardiac surgery (Level of Evidence: C)

- Class IIb
  - MV surgery may be considered in symptomatic patients with chronic severe primary MR and LVEF ≤ 30% (Level of Evidence: C)
  - MV repair may be considered in patients with rheumatic MV disease when surgical treatment is indicated if a durable and successful repair is likely or when long term reliability of anticoagulation management is questionable (Level of Evidence: B)
  - Transcatheter MV repair may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal goal directed medical therapy (GDMT) for heart failure (HF) (Level of Evidence: B)

- Class III: Harm
  - MV replacement should not be performed in isolated severe primary MR limited to less than ½ the posterior leaflet pathology unless MV repair has been attempted and was unsuccessful (Level of Evidence: B)

Secondary MR

- Mitral valve is structurally normal
- MR is due to left ventricular dysfunction
  - Ischemic
    - Papillary muscle displacement leading to leaflet tethering
  - Dilated
    - Annular dilation leading to failure of coaptation

Stages of Secondary MR

- Table 21-4
- Severe secondary MR is defined by EROA ≥ 0.4 cm^2 (same as primary MR)
  - The PISA method by 2D TTE in patients with secondary MR underestimates the true EROA because of the crescentic shape of the proximal convergence

TABLE 21-4

STAGES OF SECONDARY MR

STAGE	VALVE ANATOMY	DEFINITION	VALVE HEMODYNAMICS	ASSOCIATED CARDIAC FINDINGS	SYMPTOMS
A	At risk of MR	Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	No MR jet or small central jet area <20% LA Small vena contracta <0.3 cm	Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities Primary myocardial disease with LV dilation and systolic dysfunction	Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	Regional wall motion abnormalities with mild tethering of mitral leaflet Annular dilation with mild loss of coaptation of the mitral leaflets	ERO <0.4 cm^2 Regurgitant volume <60 mL Regurgitant fraction ≤50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO≥0.4 cm^2 Regurgitant volume ≥60 mL Regurgitant fraction ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO≥0.4 cm^2 Regurgitant volume ≥60 mL Regurgitant fraction ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	HF symptoms due to MR persist even after revascularization and optimization of medical therapy Decreased exercise tolerance Exertional dyspnea

Nishimura et al. J am coll cardiol. 2017;70:252–289

Diagnosis and Follow-up

- Class I
  - TTE is useful for establish the etiology of chronic secondary MR (stages B to D) and the extent and location of wall motion abnormalities and to assess global LV function, severity of MR and magnitude of pulmonary hypertension (Level of Evidence: C)
  - Noninvasive imaging (stress nuclear/positron emission tomography, CMR or stress echocardiography), cardiac computed tomography (CT) angiography, or cardiac catheterization, including coronary arteriography, is useful to establish etiology of chronic secondary MR (stages B to D) and/or to assess myocardial viability, which in turn may influence management of functional MR (Level of Evidence: C)

Management of Secondary MR

- Class I
  - Medical therapy for secondary MR should receive standard HF GDMT (ACEI/ARB/sacubitril-valsartan, beta blocker, spironolactone) (Level of Evidence: A)
  - Cardiac resynchronization therapy (CRT) recommended when indications are met (Level of Evidence: A)
- Class IIa
  - Mitral valve surgery is reasonable for patients with chronic severe MR undergoing coronary artery bypass grafting (CABG) or aortic valve replacement (AVR) (Level of Evidence: C)
  - It is reasonable to choose chordal sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA III to IV) with chronic severe MR (stage D) and persistent symptoms despite GDMT for HF (Level of Evidence: B)
- Class IIb
  - Mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF. (Level of Evidence: B)
  - In patients with chronic, moderate, ischemic MR (stage B) undergoing CABG, the usefulness of MV repair is uncertain (Level of Evidence: B)

The summary of indications for surgery in MR are summarized in Fig. 21-7.

TRICUSPID VALVE DISEASE

Tricuspid Valve Anatomy

- The tricuspid valve is more apically displaced than the mitral valve and has a larger orifice than the mitral valve
- Three leaflets
  - Anterior
  - Posterior
  - Septal
- Each leaflet has its own papillary muscle, but in 20% of individuals—no distinct septal papillary muscle

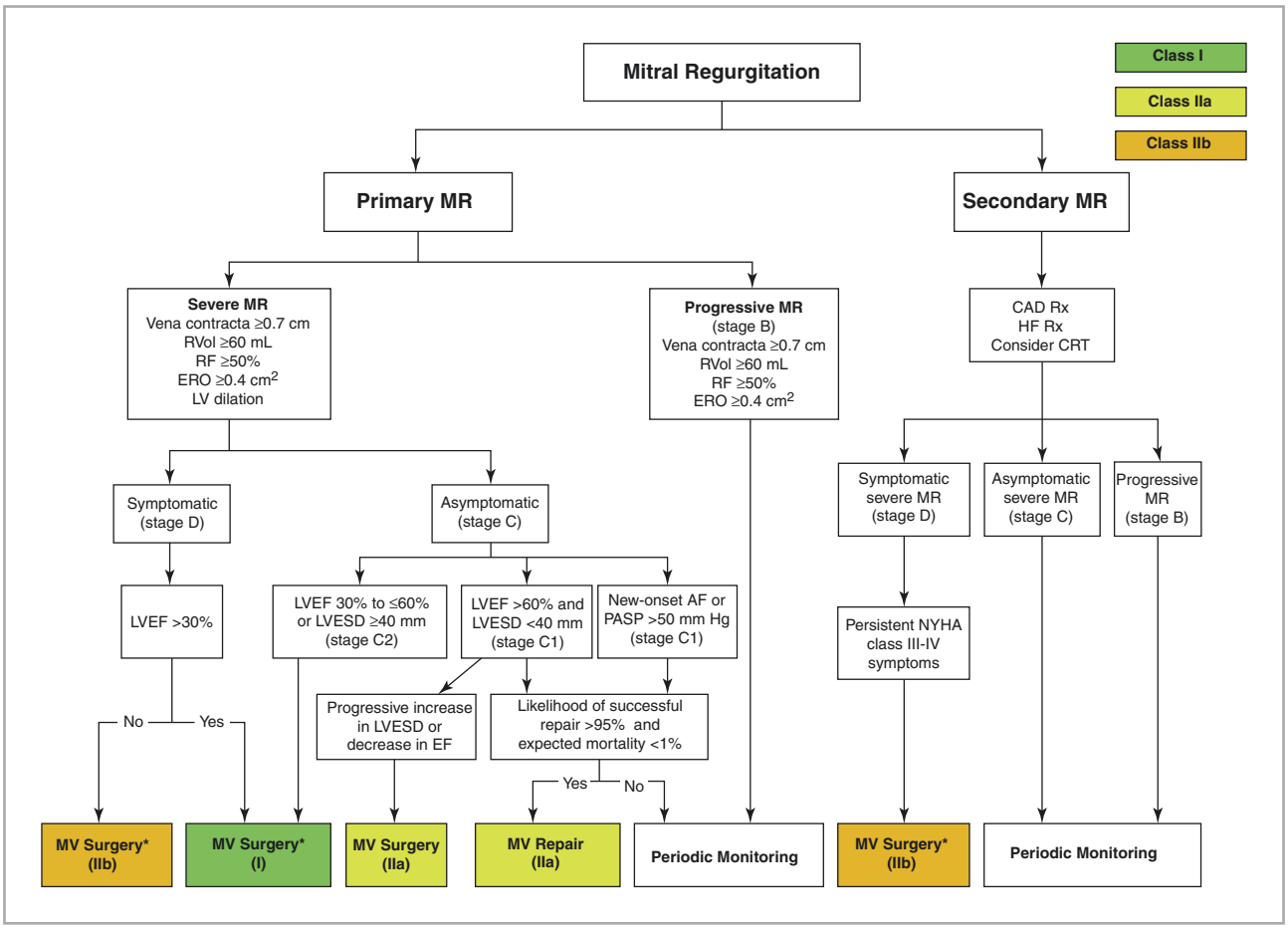

FIGURE 21-7

Indications for surgery for MR. *AF* atrial fibrillation, *CAD* coronary artery disease, *CRT* cardiac resynchronization therapy, *EF* ejection fraction, *ERO* effective regurgitant orifice, *HF* heart failure, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic diameter, *MR* mitral regurgitation, *MV* mitral valve, *NYHA* New York Heart Association, *PASP* pulmonary artery systolic pressure, *RF* regurgitant fraction, *RVol* regurgitant volume, *Rx* therapy. Source: Nishimura et al. J Am Coll Cardiol. 2017;70:252–289

  - Instead, a group of muscles

- Integrity of annulus related to right ventricular size and systolic function
  - Hence substrate for secondary TR

Tricuspid Stenosis

- Causes increased RA pressures with progressive RA dilation

Etiology:

- Rheumatic heart disease (rarely isolated stenosis, usually results in mixed stenosis/regurgitation; almost always mitral valve also involved)
- Rare:

- Infective endocarditis
- Ebstein's anomaly
- Carcinoid
- Loeffler endocarditis
- Tumor (mechanical obstruction)
- Fabry's disease

Clinical Assessment

- History
  - Symptoms of TS are very nonspecific and include those of congestion of the right heart
    - Neck fluttering or fullness
    - Fatigue
    - Abdominal fullness, particularly in the right upper quadrant
    - Protein losing enteropathy is more common in TS
- Physical examination (see Chap. 1 for further details)
  - Physical findings in TS include marked elevation of neck veins, cannon A waves, as well as a mid-diastolic rumbling murmur that increases with inspiration

Echocardiographic Appearance

- Thickening and/or calcification
- Restricted mobility with diastolic doming of anterior leaflet

- Hemodynamically significant tricuspid stenosis (TS) / severe TS
  - Specific findings
    - Mean pressure gradient ≥5 mmHg
    - Inflow velocity-time integral >60 cm
    - Pressure half time >190 ms
    - Valve area by continuity equation ≤ 1.0 cm^2
  - Supportive findings
    - Enlarged RA ≥ moderate
    - Dilated inferior vena cava

Diagnosis and Follow-up

- Class I
  - TTE is indicated in patients with TS to assess the anatomy of the valve complex, evaluate severity of stenosis, and characterize any associated regurgitation and/or left-sided valve disease (Level of Evidence: C)
- Class IIb
  - Invasive hemodynamic assessment of severity of TS may be considered in symptomatic patients when clinical and noninvasive data are discordant (Level of Evidence: C)

Management:

- Manage fluid status and any left sided heart disease
- Class I

- TV surgery is indicated for patients with isolated severe TS (Level of Evidence: C)
- TV surgery recommended for severe TS at the time of left heart surgery (Level of Evidence: C)

■ Class IIb

- Percutaneous balloon tricuspid commissurotomy might be considered in patients with isolated, symptomatic, severe TS without accompanying tricuspid regurgitation (TR) (Level of Evidence: C)

Tricuspid Regurgitation

■ Clinically insignificant TR is detected in many healthy individuals

- Mild TR: up to 60%
- Moderate TR: up to 15%

■ TR severity affects mortality

- Fig. 21-8

Stages of TR

■ Table 21-5

Etiology of TR

■ Primary (valvular)

- Congenital
  - ■ Ebstein's anomaly
    - Apical displacement of the annulus of the septal and anterior leaflets of TV
    - Atrialization of RV
    - Accompanying lesions may include:
      - ■ Ventricular inversion
      - ■ Atrial septal defect / patent foramen ovale
      - ■ Ventricular septal defect
      - ■ Pulmonic stenosis

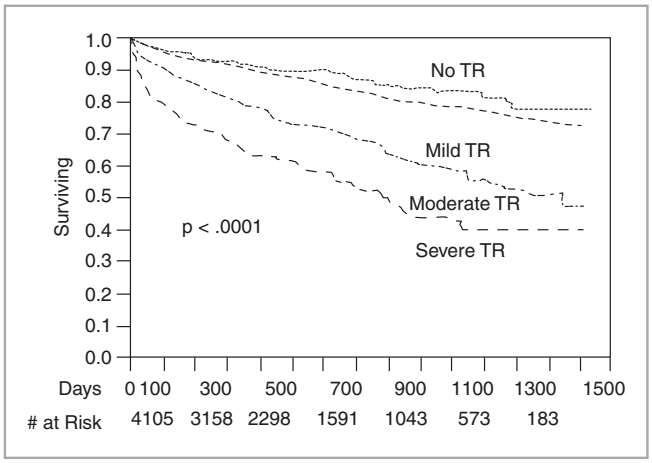

FIGURE 21-8

Impact on TR on survival. Source: Nath et al. J Am Coll Cardiol. 2004;43:405–409

TABLE 21-5

STAGES OF TR

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	At risk of TR	Primary: *Mild rheumatic change* *Mild prolapse* *Other (e.g. IE with vegetation, early carcinoid deposition, radiation)* *Intra-annular RV pacemaker or ICD lead* *Post cardiac transplant (biopsy related)* Functional: *Normal* *Early annular dilation*	No or trace TR	None	None or in relation to other left heart or pulmonary/pulmonary vascular disease
B	Progressive TR	Primary: *Progressive leaflet deterioration/destruction* *Moderate-to-severe prolapse, limited chordal rupture* Functional: *Early annular dilation* *Moderate leaflet tethering*	Mild TR: *Central jet area <5 cm²* *Vena contracta width not defined* *CW jet density and contour: soft and parabolic* *Hepatic vein flow: systolic dominance* Moderate TR: *Central jet area 5–10 cm²* *Vena contracta width not defined but <0.7 cm* *CW enisty and contour: dense, variable contour* *Hepatic vein flow: systolic blunting*	Mild TR: *RV/RA/IVC size normal* Moderate TR: *No RV enlargement* *No or mild RA enlargement* *No or mild IVC enlargement with normal respiropha-sic variation* *Normal RA pressure*	None or in relation to other left heart or pulmonary/pulmonary vascular disease

TABLE 21-5

(CONTINUED)

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
C	Asymptomatic severe TR	Primary: *Flail or grossly distorted leaflets* Functional: *Severe annular dilation (>40 mm or 21 mm/m²)* *Marked leaflet tethering*	Central jet area >10 cm² Vena contracta width >0.7 cm CW jet density and contour: dense, triangular with early peak Hepatic vein flow: systolic reversal	RV/RA/IVC dilated with decreased IVC respirophasic variation Elevated RA pressure with "c-V" wave Diastolic interventricular septal flattening may be present	None, or in relation to other left heart or pulmonary/pulmonary vascular disease
D	Symptomatic severe TR	Primary: *Flail or grossly distorted leaflets* Functional: *Severe annular dilation (>40 mm or 21 mm/m²)* *Marked leaflet tethering*	Central jet area >10 cm² Vena contracta width >0.7 cm CW jet density and contour: dense, triangular with early peak Hepatic vein flow: systolic reversal	RV/RA/IVC dilated with decreased IVC respirophasic variation Elevated RA pressure with "c-V" wave Diastolic interventricular septal flattening Reduced RV systolic function in late phase	Fatigue, palpitations, dyspnea, abdominal bloating, anorexia, edema

Source: Nishimura et al. J Am Coll Cardiol. 2014;63:e57–e185

- Rheumatic (MV often involved as well)
- Infectious endocarditis
  - Intravenous drug use
  - Alcoholism
  - Neoplasms
  - Infected intravenous catheters
- Carcinoid heart disease
  - Affects 20% of people with carcinoid
    - Flushing, diarrhea
  - Echocardiographic findings
    - TS/TR
      - Shortened and thickened TV leaflets
      - Moderate to severe TR in 90% patients
      - Pulmonary valve involvement in 90% patients
      - (PR 81%, PS 53%)

- Degenerative
  - TV prolapse

- Secondary (ventricular)
  - 80% of important TR is 'functional'
    - Dilation of the RV cavity and tricuspid valve annulus; leaflet tethering
    - Often secondary to effects of left-sided heart diseases
    - Pulmonary hypertension
      - Pulmonary artery systolic pressure > 50 mmHg
  - Cor pulmonale
  - Inferior/RV myocardial infarction
  - Left sided pathology
    - Degenerative mitral valve
    - LV dysfunction
  - Atrial fibrillation has also been linked to the development of tricuspid regurgitation via tricuspid annular dilation

Clinical Assessment

- History
  - Symptoms from TR are rare unless severe regurgitation is present.
  - If symptomatic, complaints related to right heart failure predominate, as with TS.

- Physical examination (see Chap. 1 for more details)
  - The jugular venous pressure is usually elevated, with a prominent 'v' wave
    - This may lead to overestimation of filling pressures if TR is not recognized.
  - A low frequency holosystolic murmur along the left sternal border is typically present.
    - This murmur increases with inspiration.
  - Parasternal heave and a right-sided S3 gallop (increasing with inspiration) may also be present.
  - A pulsatile liver is frequently palpable in severe TR; if not, cirrhosis may be present.
  - Lower extremity edema

Diagnosis and Follow-up

- Class I
  - TTE is indicated to evaluate severity of TR, determine etiology, measure sizes of right-sided chambers and inferior vena cava, assess RV systolic function, estimate pulmonary artery systolic pressure, and characterize any associated left-sided heart disease (Level of Evidence: C)

- Class IIa
  - Invasive measurement of pulmonary artery pressures and pulmonary vascular resistance can be useful in patients with TR when clinical and noninvasive data regarding their values are discordant (Level of Evidence: C)

- Class IIb
  - CMR or real-time 3D echocardiography may be considered for assessment of RV systolic function and systolic and diastolic volumes in patients with severe TR (stages C and D) and suboptimal 2D echocardiograms (Level of Evidence: C)
  - Exercise testing may be considered for the assessment of exercise capacity in patients with severe TR with no or minimal symptoms (stage C) (Level of Evidence: C)
- Doppler signs of severe TR
  - TR jet area > 10 cm^2
  - Systolic flow reversal in the hepatic veins
  - Vena contracta width >7 mm
    - Typically performed in apical view
    - Narrowest neck of regurgitant flow just distal to the flow convergence region
  - PISA radius > 9 mm
  - EROA ≥ 40 mm^2
  - Supporting findings
    - Dense continuous wave Doppler signal
    - Annular dilation > 4 cm
    - Increased tricuspid E wave velocity > 1 m/s

Medical Management of TR

- Class IIa
  - Diuretics can be useful for patients with severe TR and signs of right heart failure (stage D) (Level of Evidence: C)
- Class IIb
  - Medical therapies to reduce elevated pulmonary artery pressures and/or pulmonary vascular resistance might be considered in patients with severe functional TR (stages C and D) (Level of Evidence: C)

Surgery for TR

- Class I
  - Tricuspid valve surgery is recommended for patients with severe TR (stages C and D) undergoing left-sided valve surgery (Level of Evidence: C)
- Class IIa
  - Triscupid valve repair can be beneficial for patients with mild, moderate, or greater functional TR (stage B) at the time of left-sided valve surgery with either
    - Tricuspid annular dilation (>40 mm diameter, or >21 mm/m^2 indexed on TTE, or >70 mm diameter on direct intraoperative measurement) (Level of Evidence: C)
    - Prior evidence of right heart failure (Level of Evidence: C)
  - Tricuspid valve surgery can be beneficial for patients with symptoms due to severe primary TR that are unresponsive to medical therapy (stage D) (Level of Evidence: C)

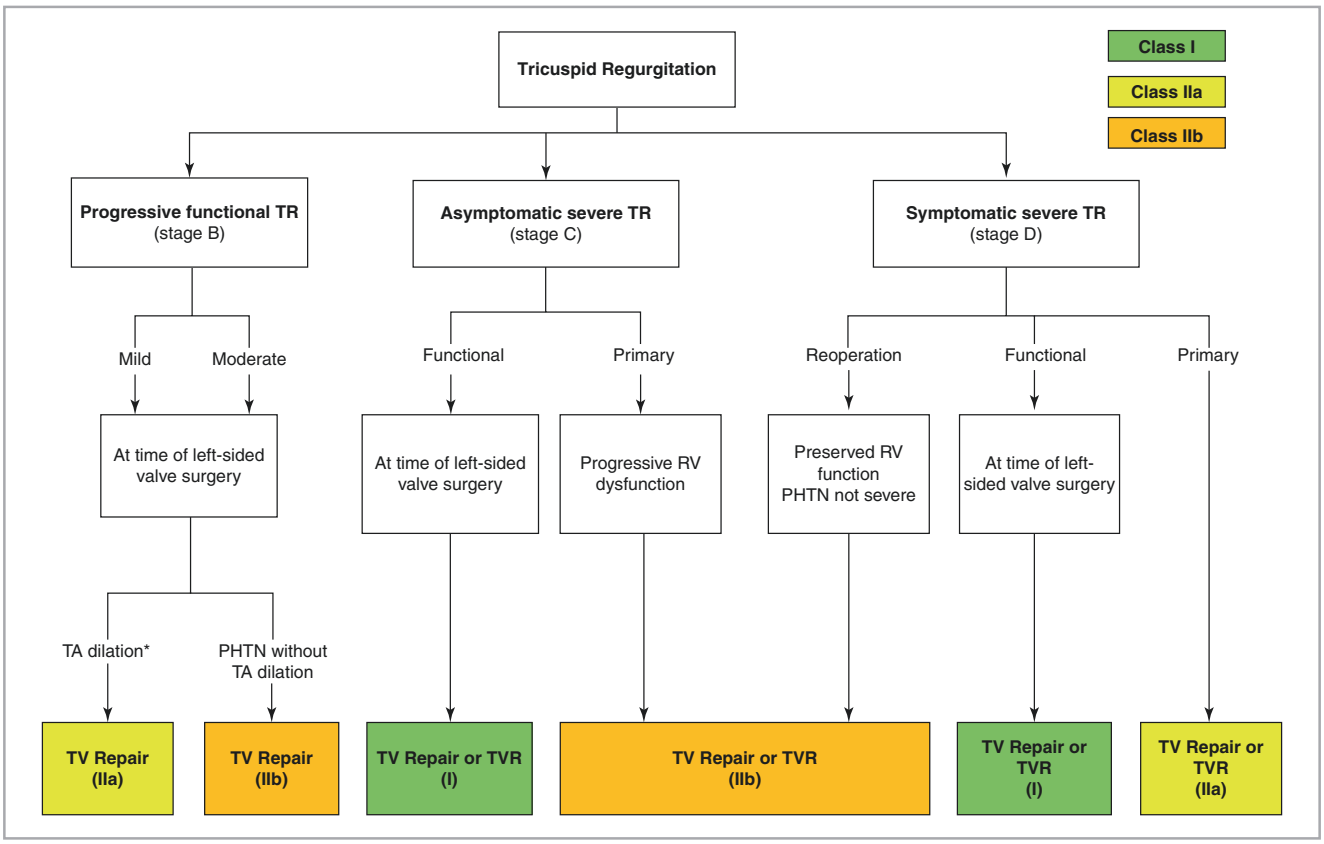

FIGURE 21-9

Indications for surgery for TR. TA dilation is defined by >40 mm on TTE (>21 mm/m^2) or >70 mm on direct intraoperative measurement. *LV* left ventricular, *PHTN* pulmonary hypertension, *RV* right ventricular, *TA* tricuspid annular, *TR* tricuspid regurgitation, *TTE* transthoracic echocardiogram, *TV* tricuspid valve, *TVR* tricuspid valve replacement. Source: Nishimura et al. J Am Coll Cardiol. 2014;63:e57–e185

- Class IIb
  - TV repair may be considered for patients with moderate functional TR (stage B) and pulmonary artery hypertension at the time of left-sided valve surgery (Level of Evidence: C)
  - TV surgery may be considered for asymptomatic or minimally symptomatic patients with severe primary TR (stage C) and progressive degrees of moderate or greater RV dilation and/or systolic dysfunction (Level of Evidence: C)
  - Reoperation for isolated tricuspid valve repair or replacement may be considered for persistent symptoms due to severe TR (stage D) in patients who have undergone previous left-sided valve surgery and who do not have severe pulmonary hypertension or significant RV systolic dysfunction (Level of Evidence: C)
- The number of operations for isolated tricuspid valve repair and replacement is increasing, although operative mortality remains unchanged (Zack et al. J Am Coll Cardiol. 2017; 70:2953–2960)
- Summary of indications for surgery for TR (Fig. 21-9)

Questions

1. A 65 year old woman presents with worsening exertional dyspnea. Precordial auscultation reveals a late-diastolic murmur at the apex in addition to a soft pan-systolic murmur. There is no jugular venous distention and the chest is clear to auscultation. Echocardiography reveals normal left ventricular systolic function (LVEF >60%) and mitral stenosis is noted with a MV area is measured at 1.3 cm^2. There is also mild-to-moderate MR and a moderately dilated LA.

   Which of the following statements is most correct?

   a. Slowing heart rate will not benefit symptoms
   b. The decision to pursue surgical or transcatheter intervention is unaffected by whether the MS is caused by rheumatic change or senile calcific change
   c. The presence of mild-to-moderate MR precludes percutaneous mitral balloon commissurotomy as an option for this patient
   d. The patient's mitral valve area is consistent with severe MS

2. A 60 year old man is found to have an apical pansystolic murmur on physical examination. He is asymptomatic but is found on echocardiography to have MR with regurgitant volume 75 mL. LVEF is 58%, LVESD is 42 mm. The mechanism is isolated posterior leaflet prolapse. Blood pressure is 125/78 mmHg, heart rate is 72 bpm. Body mass index is within normal limits. The patient is seen at a heart valve center of excellence.

   Which of the following statements is false?

   a. MV repair is preferred to replacement
   b. If the anterior leaflets were also involved, mitral valve replacement is preferred
   c. The patient meets class I indication for surgical intervention
   d. The patient should receive MV surgical intervention if undergoing another type of cardiac surgery

3. A 64 year old woman with a history of idiopathic dilated cardiomyopathy presents for a second opinion. Current medications include carvedilol, ramipril furosemide, magnesium, potassium and spironolactone which she has been taking for two years. ECG shows sinus rhythm with left bundle branch block. Physical examination reveals a non-elevated jugular venous pressure, a displaced apical impulse and a pansystolic murmur. Blood pressure is 100/78 mmHg, heart rate is 68 bpm. Height is 5 feet, 6 inches. Weight is 130 lbs. Echocardiography reveals severe MR. LVEF is 30%. LV end-systolic dimension is 49 mm. The mitral annulus is dilated.

   Which of the following statements is most correct?

   a. Cardiac resynchronization is indicated
   b. The patient should receive mitral valve replacement
   c. The patient should receive annuloplasty repair
   d. Transcatheter mitral valve intervention should be performed

4. A 61 year old man has severe MR. He is clinically euvolemic and normotensive on examination. A pansystolic murmur is heard across the precordium. In addition to his MR, the tricuspid annulus is dilated on echocardiography and a degree of TR is noted. The final determination of TR severity is pending. The patient is planned for surgical intervention to the mitral valve.

   Which of the following is least correct?

   a. The patient should have tricuspid valve repair at the time of mitral surgery if TR is severe
   b. The patient should have tricuspid valve repair at the time of mitral surgery if TR is moderate
   c. It is reasonable to consider intervention to the tricuspid valve at the time of mitral surgery if TR is mild and the tricuspid annulus measures 45 mm
   d. Tricuspid valve repair is not beneficial for patients with functional TR and prior evidence of right heart failure

Answers

1. **Correct answer: d**

   MV area ≤1.5 cm^2 is consistent with severe MS, whilst MV area ≤1.0 cm^2 is consistent with very severe MS, hence the patient's MV area of 1.3 cm^2 classifies them as having severe MS, making option d correct. Slowing heart rate can benefit patients with exertional symptoms in the presence of MS by allowing longer diastolic filling time of the LV (option a). There is no current recommendation for surgical or transcatheter intervention in senile calcific MS, but there is in rheumatic MS, so etiology is important in considering the decision to intervene (option b). The presence of mild-to-moderate MR is important to weigh if percutaneous mitral balloon commissurotomy is being considered, however it does not preclude this as an option (option c).

2. **Correct answer: b**

   In a center of excellence, where the likelihood of successful repair is high, repair is still preferred over replacement even if the anterior and posterior leaflets are both involved (option b is therefore a false statement). Options a, c and d are true statements, making them incorrect.

3. **Correct answer: a**

   This patient meets standard indication for CRT, and hence also meet Class I indication from a MR perspective as they have been on goal directed HF therapy and remain with severe MR. The decision to perform intervention in secondary MR (options b–d) require knowledge of the patient's symptoms, which we do not have. In any case, CRT would be indicated before surgical or transcatheter intervention is considered. Thus, option a is the most correct.

4. **Correct answer: d**

   Tricuspid valve repair can be beneficial in the presence of functional TR (mild, moderate or severe) with prior evidence of right heart failure. Thus, option d is the least correct statement, making it the correct answer. Severe TR is a class I indication for tricuspid valve surgery at the time of left heart surgery (option a), whilst moderate TR is a class IIa indication (option b). Mild TR in the presence of a dilated annulus (>40 mm) is also a class IIa indication for intervention at the time of left heart surgery (option c).

Further Reading

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CHAPTER 22

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Infective Endocarditis and Device Infections

CHAPTER OUTLINE

INFECTIVE ENDOCARDITIS (IE)

An infection of the endocardium which most frequently involves the heart valves but can also include chamber walls, chordae, and prosthetic material [1]

A) Epidemiology and Risk Factors

- 10–20% of IE cases occur in those without prior cardiac disease [1, 2]
- Degenerative valvular heart disease is a common predisposing condition in the modern era [2]
- Up to 25% of IE cases in a large international cohort have been linked to nosocomial exposure [2]
- Rates of IE in the United States continue to increase to approximately 15 per 100,000 in 2011, up from 9.3 per 100,000 in 1998 [3]. The epidemiology of IE has shifted over the past several decades with increasing frequency of *Staphylococcus aureus*, likely as a result of increasing numbers of invasive procedures and injection drug users (IDU)
- Community-acquired endocarditis accounts for ~70% of cases
- The burden of IE among IDU is increasing rapidly [4, 5]; for example, in a single-center study at an academic medical center, the proportion of IE attributed to IDU increased from 15% in 2009 to 56% in 2014 [5].

- *Staphylococcus aureus* is most common pathogen and an important risk factor for mortality [6].
- Polymicrobial or unusual pathogens are also more common in IDU with IE
- Right-sided IE is particularly common in IDU who may present with symptoms such as right-sided heart failure due to tricuspid insufficiency or pleuritic chest pain from septic emboli

B) **Clinical Presentation and Diagnosis**

- IE is a heterogeneous disease with a wide range of clinical presentations, so a high index of suspicion and thorough, multidisciplinary diagnostic evaluation is often needed
- **Clinical signs and symptoms:** Most common findings in an international cohort of IE [2]:
  - Fever (96%)
  - New murmur (48%)
  - Worsening of pre-existing murmur (20%)
  - Hematuria (26%)
  - Vascular embolic event (17%)
- **ECG**: Prolongation of PR interval and development of AV nodal block can indicate perivalvular/aortic root infection extension involving the His-Purkinje system (usually in the case of aortic valve endocarditis).
- **Echocardiography:** Characteristics suggestive of vegetation(s) [7]
  - Location: At sites of a high velocity jet and non-laminar flow, particularly when associated structural defects such as ventricular septal defect or foreign material such as a prosthetic heart valve are present
  - Motion: Independent of the valve
  - Shape: Amorphous
  - Texture: When fresh, less echodense than calcium and the myocardium; aging vegetations usually increase in echodensity due to tissue organization of the vegetation
  - Echocardiography should always assess for structural complications of endocardial infection: abscesses, perivalvular pseudoaneurysms, tissue perforation, valve aneurysms, and fistula formation
  - Serial echocardiograms can be useful in the setting of high pre-test probability and an initially negative study
- TTE is appropriate as an initial test for suspected endocarditis, however sensitivity for endocarditis in prosthetic valves is low (Table 22-1)
- TEE is appropriate when TTE is non-diagnostic or when suspicion for endocarditis is high especially in the case of prosthetic valves, intra-cardiac device, staph aureus bacteremia or fungemia [8]
- TEE may be better able to visualize structural complications of endocarditis
- PET-CT has an emerging role in the diagnosis of IE and may be more sensitive than TEE for detecting prosthetic valve endocarditis, particularly perivalvular abscess [9].
- Multislice CT can be used to detect abscesses/pseudoaneurysms with diagnostic accuracy similar to TEE [7]

Table 22-1.

C) **Microbiology and Pathology:**

- Blood cultures *prior* to antimicrobial initiation are imperative for IE diagnosis
- Optimally, 3 sets (= 6 bottles; 1 set is composed of 1 aerobic and 1 anaerobic bottle) of blood cultures from different access sites are obtained over 24 hours (at least 20 cc in each blood culture bottle for improved yield in adults)

- Histologic findings on cardiac valves after surgical resection can be diagnostic [10], including the specific pattern of inflammation [11]
  - However, positive histopathology stains can persist in sterile vegetations
  - Tissue culture can be helpful [12] but must be interpreted with caution as there can be high rates of contamination [10]

Current standard of care for diagnosis is the modified Duke criteria (Table 22-2)
Table 22-2.
Table 22-3.

D) Treatment

Prompt initiation of parenteral antimicrobials is the mainstay of treatment, in conjunction with surgical evaluation when indicated (see section F).
Table 22-4

E) Complications

IE can pursue a fulminant or subacute clinical course that depends on host, pathogen and the rapidity of diagnosis, treatment initiation, and presence of complications from the endovascular infection.

TABLE 22-1

SENSITIVITY AND SPECIFICITY OF ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS [1]

	SENSITIVITY	SPECIFICITY
Native valve		
TTE	60–65%	90–98%
TEE	85–95%	90–98%
Prosthetic valve		
TTE	<50%	90–98%
TEE	82–90%	90–98%

TABLE 22-2

DEFINITION OF INFECTIVE ENDOCARDITIS ACCORDING TO THE MODIFIED DUKE CRITERIA [7, 13]

Definite infective endocarditis
Pathologic criteria
(1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
(2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
Clinical criteria
(1) 2 major criteria; or
(2) 1 major criterion and 3 minor criteria; or
(3) 5 minor criteria

Possible infective endocarditis
(1) 1 major criterion and 1 minor criterion; or
(2) 3 minor criteria

Rejected
(1) Firm alternate diagnosis explaining evidence of infective endocarditis; or
(2) Resolution of infective endocarditis syndrome at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or
(3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or
(4) Does not meet criteria for possible infective endocarditis, as above

TABLE 22-3

DEFINITION OF TERMS USED IN THE MODIFIED DUKE CRITERIA FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS (IE) [7, 13]

Major criteria

Blood culture positive for IE:

Typical micro organisms consistent with IE from 2 separate blood cultures: Viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus;* or community-acquired Enterococci in the absence of a primary focus

OR

Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:

At least 2 positive cultures of blood samples drawn > 12 h apart or all 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart) or single positive blood culture for *Coxiella burnetii* or IgG antibody titer > 1:800

Evidence of endocardial involvement:

Echocardiogram positive for IE∗, defined as follows:

Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation

or

Abscess

or

New partial dehiscence of prosthetic valve

or

New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

∗TEE recommended for patients with prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE (paravalvular abscess)

Minor criteria

Predisposition, predisposing heart condition, or IDU

Fever (temperature > 38°C)

Vascular phenomena:

Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

Immunologic phenomena

Glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor

Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serologic evidence

TABLE 22-4

GUIDELINES FOR ANTIBIOTIC SELECTION AND TREATMENT DURATION FOR NATIVE VALVE ENDOCARDITIS [13]

PATHOGEN	ANTIMICROBIAL	DURATION (WEEKS)
Streptococci (viridans group or bovis)		
Dosing depends on MIC to penicillin	Penicillin or Ceftriaxone OR	4
	Penicillin or Ceftriaxone + Gentamicin OR	2
	Vancomycin (Penicillin -allergic)	4
If MIC for penicillin >0.5 ug/mL	Use Enterococcal IE guidelines	
Staphylococci		
If oxacillin-susceptible∗	Nafcillin or oxacillin; Cefazolin is an alternative for penicillin-allergic	6
If oxacillin-resistant or for penicillin-allergic patients	Vancomycin (for beta-lactam allergic) or Daptomycin 8 mg/kg (higher doses may be preferred)	6
Enterococcus (if susceptible to penicillin, Gentamicin, and Vancomycin; in cases of resistance, Infectious Disease consultation)	Ampicillin or penicillin + Gentamicin OR	4–6
	Ampicillin + Ceftriaxone (esp if GFR < 50)	6

TABLE 22-4

(CONTINUED)

PATHOGEN	ANTIMICROBIAL	DURATION (WEEKS)
VRE	Linezolid or Daptomycin 10–12 mg/kg	>6
HACEK**	Ceftriaxone OR Ampicillin-sulbactam OR Ciprofloxacin (penicillin-allergy)	4
Culture-negative	Ampicillin-sulbactam + Gentamicin OR Vancomycin + Gentamicin + Ciprofloxacin	4–6
Culture-negative (suspected *Bartonella*)	Ceftriaxone + Gentamicin +/– Doxycycline (Gentamicin can be discontinued at 2 weeks)	6

*Oxacillin-susceptibility should be confirmed with the microbiology lab as some Staphylococcal spp have heteroresistance and require screening for *mecA* gene

**_Haemophilus parainfluenza, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,_ and _Kingella kingae_

■ Heart failure (HF)

- HF is the most frequent complication of IE and most common indication for surgery given increased rates of morbidity and mortality
- Predominantly caused by severe aortic or mitral regurgitation from leaflet perforation, leaflet malcoaptation due to vegetation, or mitral chordal rupture; less commonly by fistulae and obstruction from large vegetations
- Surgery should be performed on an *emergent* basis in cases of persistent pulmonary edema or cardiogenic shock and should be performed *urgently* when NYHA class III-IV heart failure is present or there is severe aortic or mitral valve dysfunction without clinical heart failure [7]
- The Society of Thoracic Surgeons endocarditis score and De Feo et al score have been developed to predict operative mortality after surgery for active IE [14, 15]

■ Embolization

- Evident in 20–50% of IE cases and associated with increased morbidity and mortality [7]
- The brain and spleen are the most frequent sites of embolism in left-sided IE; pulmonary emboli are frequent in right-sided and pacemaker lead IE [7]. Emboli to the bowel, kidneys, spine, coronary arteries, and extremities can also be seen in left-sided IE.
- Asymptomatic CNS emboli incidentally found on imaging are frequent (35–60% of IE patients) [16, 17]
- After initial 2–3 weeks of antimicrobials, embolic events become much less frequent / likely [18]
- Risk factors for embolization include: larger vegetation size, mitral valve involvement, *Staphylococcal* species, prior embolization [19, 20]
- Mycotic aneurysms can form intracranially or extracranially; if intracranially, mycotic aneurysms can cause focal neurologic deficits that, in cases of progression or rupture, require surgical or endovascular treatment
- Timing of surgery in patients with CNS emboli must be balanced carefully with the surgical risk and risk for intracranial hemorrhage while on bypass with need for high dose IV heparin [20, 21]
- Intracranial hemorrhage remains an uncommon but devastating complication (~5%) and is a contraindication to surgical intervention [12, 22]

F) Surgery for IE

Although surgical intervention must always be individualized with guidance ideally from a multidisciplinary team, guidelines suggest specific indications for surgical intervention [7, 13]. Randomized controlled trial data and retrospective observational studies favor early surgery when feasible to reduce embolic complications and to potentially reduce mortality.

Post-operative infection of new prostheses is rare (2–3%) even when surgical intervention is performed in active IE [23]. Cases associated with IDU present a particularly challenging situation in which reinfection rates may be higher [24] and multidisciplinary assessment including addiction specialists may aid in decision making.

Table 22-5

Table 22-6

G) Outcomes and follow-up

- Almost 50% of patients with IE require surgical intervention [2]
- Inpatient mortality has been found to be 15–20% [2]
  - Risk factors for death include increasing age, HF, paravalvular complications, prosthetic valve endocarditis, and *Staphylococcus aureus* as the causative organism [7]

TABLE 22-5

CLINICAL AND ECHOCARDIOGRAPHIC FINDINGS THAT SUPPORT NEED FOR SURGICAL INTERVENTION [7, 13]

VEGETATION	VALVULAR DYSFUNCTION	INVASIVE INFECTION
Persistent vegetation after systemic embolization	Acute aortic or mitral insufficiency with signs of ventricular failure	Valvular dehiscence, rupture, or fistula
Anterior mitral leaflet vegetation, particularly if >10 mm	Heart failure that is unresponsive to medical management	New heart block
≥ 1 embolic events during first 2 weeks of antimicrobial therapy		Large abscess or extension of abscess despite appropriate antimicrobial therapy
Increase in vegetation size despite appropriate antimicrobial therapy		Perivalvular extension

TABLE 22-6

RECOMMENDATIONS FOR **EARLY** VALVE SURGERY IN NATIVE AND PROSTHETIC VALVE INFECTIVE ENDOCARDITIS [13]

Class I, level of evidence: B
- Heart failure due to valve dysfunction
- Fungal IE or highly resistant organisms
- Perivalvular abscess, periannular extension causing heart block, or destructive penetrating lesions
- Persistent infection (persistent bacteremia or fever lasting >5–7 days and provided that other sites of infection and fever have been excluded) after the start of appropriate antimicrobial therapy
- Prosthetic valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction

Class IIa, level of evidence: B
- ≥ 1 embolic event and persistent or enlarging vegetations despite appropriate antibiotic therapy
- Severe valve regurgitation and mobile vegetations > 10 mm

Class IIb, level of evidence: C
- Mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve and associate with other relative indications for surgery
- Increased vegetation size despite targeted antimicrobials

- Patients with IE on stable parenteral antimicrobial therapy and at low risk of complications of IE can be managed in the outpatient setting with careful monitoring and follow-up [25]
  - Dental evaluation should be performed including intraoral radiographs. Sources of oral infection should be eradicated, and good dental hygiene should be stressed [13]
  - A new baseline echocardiogram after completion of antimicrobial therapy should be performed
  - IE prophylaxis should be prescribed for appropriate procedures in patients who have recovered from IE [26]
  - In stable patients who have responded to parenteral therapy, completion of antibiotic courses with carefully selected oral regimens may be appropriate [27]. This potentially practice changing approach however will need to be validated in additional studies, and is not considered the current standard of care IE therapy

PROSTHETIC VALVE ENDOCARDITIS (PVE)

- Distinguished by early and late presentation (≤ or > 1 year post-valve implantation respectively); clinical presentation is atypical and both blood cultures and echocardiography are more often negative in PVE (Duke criteria are less sensitive in PVE) [28]
  - Most often requires surgical re-intervention because of difficulty sterilizing the prosthesis with medical therapy. PVE can be complicated by perivalvular abscess, valve dehiscence or bioprosthetic valve destruction
  - *Staphylococcus aureus* and coagulase-negative *Staphylococcus* are the most common etiologies, especially in early PVE; nosocomial pathogens are also more common than in NVE. Viridans group streptococcus is commonly seen in late prosthetic valve post-implantation IE [29]
- Antimicrobial treatment algorithms are available for PVE [12] but should be used in conjunction with Infectious Disease consultation given complexities of diagnosis and treatment in this patient population
  - High morbidity and mortality persist despite improved diagnosis, medical-surgical collaboration, and prompt treatments [29, 30]
  - TEE is almost always indicated given acoustic shadowing from prosthesis components on TTE giving a non-diagnostic result
  - PET-CT is an increasingly useful tool for identifying complications such as perivalvular abscess(es) and increases the sensitivity for detection of PVE; however, false positives findings can be seen in the early postoperative period

CULTURE NEGATIVE ENDOCARDITIS

- Divided into two major groups of patients: Those in whom cultures are negative because cultures were obtained on antibiotics, and who need antibiotics tailored to common IE pathogens, and those with endocarditis caused by fastidious organisms which are difficult or impossible to grow in culture.
- Causes [31]
  - Receipt of antimicrobials prior to collection of blood cultures
  - Right-sided endocarditis

- Endocarditis with cardiac device
- Non-bacterial pathogens (e.g. fungi, mycobacteria) or non-infectious etiologies (e.g. neoplastic, marantic endocarditis, Libman-Sacks endocarditis) where vegetations consist of fibrin and platelet aggregates
- Fastidious organisms (often intracellular) that require different diagnostic tools
  - *Coxiella burnetii* ("Q fever")-transmitted from animals via inhalation of aerosolized material from secretions, hides, etc.
  - *Bartonella* spp—transmitted from fleas or animal bites/scratches
  - *Brucella* spp—transmitted from animals via raw milk/cheese or contact with infected animal secretions
  - *Mycoplasma* spp—transmitted person to person via airborne droplets
  - *Tropheryma whippelii*—uncertain mechanism of transmission
  - Nutritionally deficient *Streptococci* (non-intracellular organism)—normal oral flora
  - HACEK organisms (*Haemophilus* spp; *Actinobacillus* spp; *Cardiobacterium hominis*; *Eikenella corrodens*; *Kingella kingae*)—normal oral flora

- Diagnosis [32]
  - Specialized culture techniques
  - Serology
  - 16S and 18S ribosomal PCR (serum, valve tissue)
    - Unfixed valve tissue should be frozen and sent for sequencing studies
- Treatment: Depends on identified etiology. If empiric treatment is required, a regimen active against most likely organisms should be formulated ideally in conjunction with an infectious disease specialist.

FUNGAL ENDOCARDITIS

- Fungal IE is an uncommon (<10%) but increasingly prevalent form of IE
  - Most commonly *Candida* spp
  - *Aspergillus* spp, *Histoplasma* spp, and other fungi can cause IE, especially in immunocompromised hosts. *Aspergillus* spp often do not grow in blood culture; biopsy and culture of embolic lesion may be necessary to establish the diagnosis
- Risk factors: prosthetic valves, nosocomial exposures, short-term catheters [33], immunocompromise, antibiotic use, IDU, TPN [33]
- Complications: most commonly embolization and large vegetations. HF and valve destruction is less common [33]
- Treatment: medical +/− surgical [13]
  - Antifungals [34]:
    - Liposomal amphotericin B +/− 5-flucytosine, generally preferred, especially for *Candida* spp. [34]
    - IV echinocandin may be an option
  - *Candida spp.* can in some cases be managed medically, but surgery is almost always required for *Aspergillus* spp.
- Recurrence rates are extremely high, so secondary prophylaxis with oral fluconazole is recommended for at least 2 years if not life-long [35–37]
- ID Consultation is strongly advised

ENDOCARDITIS PROPHYLAXIS

Table 22-7.
Table 22-8.
Table 22-9.

TABLE 22-7

CARDIAC CONDITIONS AT HIGHEST RISK FOR INFECTIVE ENDOCARDITIS (IE) [7]

Prosthetic cardiac valve or prosthetic material in valve repair
History of prior IE
Specific forms of congenital heart disease (CHD) ■ Completely repaired CHD if prosthetic material or device was placed within past 6 months ■ Repaired CHD with residual defects at or adjacent to site of prosthetic material or device ■ Unrepaired cyanotic CHD
Cardiac transplant with valvulopathy

TABLE 22-8

PROCEDURES FOR WHICH THERE ARE GUIDELINES ON INFECTIVE ENDOCARDITIS PROPHYLAXIS [7]

Dental procedures:
Any procedure that involves manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa (tooth extraction, periodontal surgery, other surgical dental procedures) [38]
Respiratory procedures:
If procedure is invasive with incision or biopsy. Not indicated in bronchoscopy.
Gatrointestinal (GI) / Genitourinary (GU) procedures:
No prophylaxis indicated.
Treatment of active GI or GU infection (if present) prior to procedure is recommended.

TABLE 22-9

RECOMMENDED ANTIBIOTIC PROPHYLACTIC REGIMEN [26]

REGIMEN	ANTIBIOTICS
Preferred	Amoxicillin 2000 mg by mouth
Penicillin allergy*	Clindamycin 600 mg by mouth OR Azithromycin 500 mg by mouth
Unable to take oral medication	Ampicillin 2g IV OR Cefazolin 1g IM or IV
Unable to take oral and penicillin allergy	Cefazolin 1g IM or IV OR Clindamycin 600 mg IM or IV

Note: all regimens are single doses to be given 30 to 60 minutes prior to procedure
*Many patients who provide a history of penicillin allergy may not be truly allergic or may no longer be truly allergic. Since beta lactams are the preferred choice for prophylaxis, it is important to seek the details of the allergy history and consider referral to an allergy specialist for help in assessing whether the patient can safely receive a beta lactam

SPECIAL TOPIC: DEVICE INFECTIONS

A) **Cardiovascular implantable electronic device (CIED) infection:** includes ICD and PPM

B) **Epidemiology:** CIED infections are a growing problem due to increasing implantation of devices in older patients with significant comorbidities

- Risk of infection is higher among patients with ICD as opposed to PPM
- CIED infections may be the result of device pocket infection tracking along the intravascular portion of the electrode or hematogenous seeding from distant focus [7]

Table 22-10

C) Clinical presentation:

- Superficial infection
- Local inflammatory changes without evidence of device involvement
- Local inflammatory changes that can progress to erosion
  - Systemic symptoms frequently absent
- Endocarditis
  - Less common but most feared
  - ~10–20% of all CIED infections

D) **Diagnosis:** [37, 39]

- IE must be suspected in unexplained fever in patients with CIED
- 2 sets of blood cultures prior to antibiotic initiation in all patients with possible CIED infection
- TTE can be helpful to determine presence of a pericardial effusion and presence of vegetation on right-sided valves or device leads
- TEE allows superior visualization of device leads including in the superior vena cava and assessment of perivalvular extension of infection
- At time of device removal:

TABLE 22-10

RISK FACTORS FOR ALL CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICE INFECTION (CIED) INFECTIONS [9]

HOST FACTORS	PROCEDURAL FACTORS	PATHOGEN FACTORS
Immunosuppression, including renal failure and steroids	"Peri-procedural factors" such as perioperative antibiotic prophylaxis	Specific microbiology of any blood stream infection in patient with CIED. (e.g. staphylococcus, streptococcus and enterococci species are most common; Gram negative bacteria less common).
Oral anticoagulation	"Operator experience"	
Patient co-morbidities	Device exchange (revision/replacement)	
Other "indwelling hardware"	Amount of indwelling hardware	
Congestive heart failure	Use of pre-procedural temporary pacing	

  - Gram stain and culture of generator-pocket-site tissue and lead tips, including anaerobic cultures
  - Fungal and mycobacterial cultures, if indicated by epidemiology or if original cultures are unrevealing
- Aspiration of the device pocket is not recommended because it is unlikely to be high yield and there is a risk of introducing infection

E) **Management:**

Table 22-11

- Complete device removal should be performed as soon as possible after CIED infection is confirmed [39]
- Given high mortality and rates of relapse, even localized device infections should be treated with complete device removal
- Duration of antibiotics is listed in Table 22-11 with the start date set at the time of device removal
- In the setting of native or prosthetic valve infection but no evidence of CIED infection, guidelines advise complete removal of the device and leads. The risks and benefits of complete extraction however should be individualized to the patient
- Percutaneous as opposed to surgical lead extraction is preferred except if percutaneous extraction is considered technically difficult, if there is severe valve destruction, or if there are large vegetations (>20 mm) [7]
- Lead age of 6 years has been associated with major perioperative complications at time of lead extraction [41]
- Blood cultures to be drawn after device removal to document sterilization
  - If blood cultures show no growth in the setting of recent antibiotics, treat as though blood cultures are positive if there is reasonable clinical suspicion
- Management of device re-implantation:
  - Assess whether the patient still requires the device: 33–50% of patients with prior CIED will no longer need CIED at time of consideration of reimplantation
  - Contralateral pocket placement, if possible
  - At least 72 hours of negative blood cultures prior to reimplantation, if possible
  - Antibiotic prophylaxis should be considered prior to reimplantation if the patient has not been maintained on antibiotics [7]
- **Suppressive antibiotics:** in setting of inability or high morbidity of device removal
  - Not recommended unless the following are all present:

TABLE 22-11

TREATMENT OF CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICE INFECTION (CIED) INFECTION [40]

TYPE OF INFECTION	MINIMUM DURATION OF ANTIBIOTICS	DEVICE
Superficial or incisional infection	7–10 days	Can be retained
Pocket infection	10–14 days	Complete removal of all hardware
CIED with erosion	7–10 days	
CIED with positive blood culture*	Minimum of 2 weeks of IV antibiotics	
Valve vegetation on TEE*	IE Guidelines	
Lead vegetation on TEE*	2–6 weeks depending on pathogen and complications	

*Id Consultation is Strongly Recommended

- Stable clinical status
- Clinical improvement after initiation of antimicrobials
- Sterilization of blood cultures

– Pursued in consultation with Infectious Disease specialists and with careful follow-up

SPECIAL TOPIC: VENTRICULAR ASSIST DEVICE (VAD) INFECTIONS

- Infection is a leading cause of morbidity and mortality in patients with VADs, although rates and outcomes are improving [42, 43]
- Guidelines for the diagnosis [44] and management [45] of VAD infections have recently been published.
- Infections can involve the pump, cannula, pocket, superficial and deep areas of the driveline, the mediastinum, and the heart valves.
- Infections are divided into categories: VAD-specific, VAD-related, and non-VAD related.

Table 22-12
Table 22-13

- **Microbiology** [46, 47]
  - Most commonly *Staphylococcal* spp (>50%)
  - Pseudomonas is second-most common (22–28%) [44]
  - Also Enterococci, gram negative rods, and *Candida* spp
- **Management** [45]
  - Surgical incision and drainage
  - Parenteral antimicrobials, often followed by oral antimicrobial suppression while VAD remains in place

TABLE 22-12

DEFINITIONS OF DIFFERENT VENTRICULAR ASSIST DEVICES (VAD) ASSOCIATED INFECTIONS [43]

VAD-specific	
	Pump and/or cannula
	Pocket infection
	Percutaneous driveline ■ Superficial ■ Deep
VAD-related	
	IE
	CVC related
	Bloodstream ■ VAD-related ■ Non VAD-related
	Mediastinitis ■ VAD related – Sternal wound – Pocket infection, continuous with mediastinum ■ Non-VAD related
Non-VAD related	e.g. lower respiratory tract infections, cholecystitis, *Clostridium difficile* infection, and urinary tract infection.

CVC Central Venous Cannula

TABLE 22-13

DEFINITIONS OF DIFFERENT MECHANICAL CIRCULATORY SUPPORT (MCS) ASSOCIATED INFECTIONS [44]

	MEDICAL INTERVENTION	SURGICAL INTERVENTION
MCS-Specific		
Pocket/ superficial DLI	2 weeks antibiotics or until resolution	
Deep DLI/ pocket	6–8 weeks antibiotics followed by oral suppression	Debridement, possible wound VAC, new exit site may be required
DLI, uncertain depth	May need to be treated as deep infection	
MCS pump and/or cannula	Empiric antibiotics for Staph *spp* and pseudomonas; Typically, 6–8 weeks with suppression to follow; duration of antibiotics per ID consultation, should continued until after transplant in BTT.	Surgical drainage and debridement may be required, including explant
Persistent bacteremia	6–8 weeks followed by suppressive antibiotics; duration per ID consultation	Explant may be required
MCS-related		
Bacteremia	*Staphylococcus aureus* 4–6 weeks; non- *Staphylococcus aureus*, consider 2 weeks from negative blood culture. If no source, may be considered pump and cannula infection (suppression may be required)	
Bacterial mediastinitis	6–8 weeks after last debridement; ID consult recommended	Debridement often indicated
IE	Treat as with MCS pump-cannula infection	May be required

BTT Bridge to Transplant, *DLI* Driveline Infection, *MCS* Mechanical Circulatory Support, *VAC* Vacuum Assisted Closure

- Varied opinions on duration of antimicrobials: patients treated with limited antimicrobials seem to have higher relapse rates but those treated with continuous antimicrobials have high risk of multi-drug resistant organisms such as Vancomycin-resistant *Enterococcus* (VRE)
- History of LVAD infection does not appear to affect post-transplant outcomes

Questions and Answers

1) A 25 year old man with a history of a cleft mitral valve with moderate mitral regurgitation is scheduled for an upcoming extraction of several teeth. When he was a child, he experienced hives after taking amoxicillin for an ear infection. In anticipation of the upcoming dental extraction, he should receive:

A. Amoxicillin 2g PO 30–60 minutes prior to the procedure
B. Clindamycin 600 mg PO
C. Azithromycin 500 mg PO x1 now followed by 250 mg PO until the procedure
D. Cefazolin 1g IM
E. No prophylaxis

1) The correct answer is E.

According to the most recent endocarditis prophylaxis guidelines, the patient does not meet any of the most at IE risk cardiac pathologies, and thus does not require antimicrobial prophylaxis prior to a higher risk dental procedure. However, if the patient would meet IE prophylaxis indications, then oral clindamycin would be the agent of choice with instructions to be taken 30–60 minutes prior to the procedure. Because of his documented allergy to penicillin (hives after amoxicillin), he should not receive the standard preferred regimen of amoxicillin 2000 mg 30–60 minutes prior to the procedure. A full course of azithromycin is not recommended, although a single dose of azithromycin can be used in penicillin-allergic patients who require prophylaxis. In case the patient is unable to take oral medications, Cefazolin IV/IM could be used as his prior allergy to penicillin resulted in hives only, which does not contraindicate cephalosporin administration.

2) A 76 year old male has had increasing fatigue over the past week. In the emergency department, he is febrile (101.0 F) and is ill-appearing with a stable II/VI harsh systolic murmur loudest at the right upper sternal border consistent with his previously diagnosed mild aortic stenosis. A careful physical exam reveals one new non-tender nodular lesion on the sole of his right foot. He is admitted to the hospital, and 2 sets of blood cultures are drawn prior to any antibiotics. Methicillin-resistant *S aureus* (MRSA) grows in 3/4 bottles at 14 hours. He has a TTE followed by a TEE that reveal no vegetation. A serum rheumatoid factor is incidentally found to be positive. What is the diagnosis and basic treatment plan?

A. Possible endocarditis; 6 weeks of IV Vancomycin
B. Possible endocarditis; 2 weeks of IV Vancomycin
C. Definite endocarditis; 6 weeks of IV Vancomycin
D. Definite endocarditis; 4 weeks of IV Linezolid
E. Not endocarditis; 2 weeks of IV Vancomycin

2) The correct answer is C.

Despite the absence of echocardiographic vegetation evidence, the patient's clinical presentation meets criteria for definite IE by the modified Duke criteria given the positive blood cultures for *S. aureus* (major criteria), fever, positive rheumatoid factor (immunologic phenomena) and a non-tender nodular lesion consistent with a Janeway lesion (3 minor criteria). Janeway lesions are microabscesses in the dermis that result from small septic emboli and are vascular phenomenon seen in IE. As a result, the patient should be treated with appropriate parenteral antibiotics with close clinical follow-up. Vancomycin remains the drug of choice in MRSA endovascular infections; linezolid is not FDA-approved for treatment of endovascular infection except for VRE.

3) A 68 year old female with a permanent pacemaker (PPM) implanted 6 years ago presents with fevers to 100.5 F and cough to her primary care physician (PCP). She is prescribed 5 days of azithromycin for tracheobronchitis but experiences no improvement in her fevers. On return to her PCP, she notes slight erythema of the soft tissue overlying the PPM site. Given concern for a late device infection, she is admitted to the hospital, where blood cultures are obtained, which show no growth. Given her potential cardiovascular implantable electronic device infection (CIED), a TEE is appropriately ordered which demonstrates a vegetation on one of the PPM leads. What are the next steps in therapeutic management?

A. Device removal alone
B. Antimicrobials; no indication for device removal
C. Device removal with concurrent antimicrobials and immediate reimplantation of CIED
D. Device removal with concurrent antimicrobials and reimplantation of CIED after 2 weeks
E. Device removal with concurrent antimicrobials and evaluation to determine if reimplantation of PPM is indicated

c) The correct answer is E.

This patient presents with a late-onset CIED infection, which requires both antimicrobial management and immediate device removal. Although blood cultures do not reveal an organism, they were obtained after initiation of antimicrobials and thus the patient required further evaluation for CIED infection with a TEE. After CIED infection is confirmed by echocardiography, immediate device removal as well as ongoing parenteral antimicrobial therapy are indicated. Given that many patients will no longer require CIED support after explanation (13–52% in several series), the patient should undergo careful evaluation regarding whether she requires reimplantation of a CIED.

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CHAPTER 23

SHAAN KHURSHID AND DAVID M. DUDZINSKI

Perioperative Cardiovascular Management

CHAPTER OUTLINE

ABBREVIATIONS

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
AHA	American Heart Association
ARB	Angiotensin receptor blocker
CAD	Coronary artery disease
DAPT	Dual antiplatelet therapy
EKG	Electrocardiogram
HDL	High density lipoprotein
ICD	Implantable cardiac defibrillator
LAD	Left anterior descending
LDL	Low density lipoprotein
LV	Left ventricle
LVEF	Left ventricle ejection fraction
MET	Metabolic equivalent
MI	Myocardial infarction
MICA	Myocardial infarction/cardiac arrest calculator
NSQIP	National Surgery Quality Improvement Program
PFO	Patent foramen ovale
RCRI	Revised cardiac risk index
RCT	Randomized controlled trial

GENERAL APPROACH [1, 2]

- Define the question
- Establish urgency
- Gather primary data
- Provide concise recommendations
- Offer contingency plans
- Offer focused recommendations within consultant's purview
- Educate, when appropriate
- Communicate directly (including to the anesthesia and surgical teams, and the patient)
- Follow up on recommendations
- For the cardiovascular consultant:
  - Conduct history and physical examination
  - Consider ancillary testing
  - Define and stratify risk based on the above
  - Implement strategies to minimize risk

RATIONALE FOR PERIOPERATIVE CARDIOVASCULAR CONSULTATION

Approximately 150,000 perioperative cardiac events (death, myocardial infarction, or stroke) occur yearly in the United States, representing 3% of all hospitalizations for noncardiac surgery [3]

- Surgery frequently exposes patients to hemodynamic stressors and a prothrombotic mileu [4]
- Cardiac complications cause over 50% of perioperative deaths
- Cardiac complications prolong hospitalization by a mean of 11 days
- Patients who suffer a perioperative MI have a 19% risk of 30-day readmission [5]
- Total national cost: estimated > $20,000,000,000 annually [6]

HISTORY

- Personal and family history of cardiovascular disease
- Traditional risk factors for cardiovascular disease
- Symptoms suggestive of cardiovascular disease: chest pain; dyspnea; palpitations; syncope; edema
- Functional capacity (Fig. 23-1, adapted from Fleisher et al. [2] and Hlatky et al. [7]):
- Relevant comorbidities
  - Pulmonary disease
  - Liver disease
  - Diabetes mellitus
  - Renal disease
  - Hematologic disorders
  - History of stroke
    - Risk of cardiac events is particularly increased within the first 9 months following ischemic stroke [8]
  - Presence of patent foramen ovale (PFO)
    - Preoperatively diagnosed PFO is associated with a 2.7-fold increase in perioperative ischemic stroke [9]

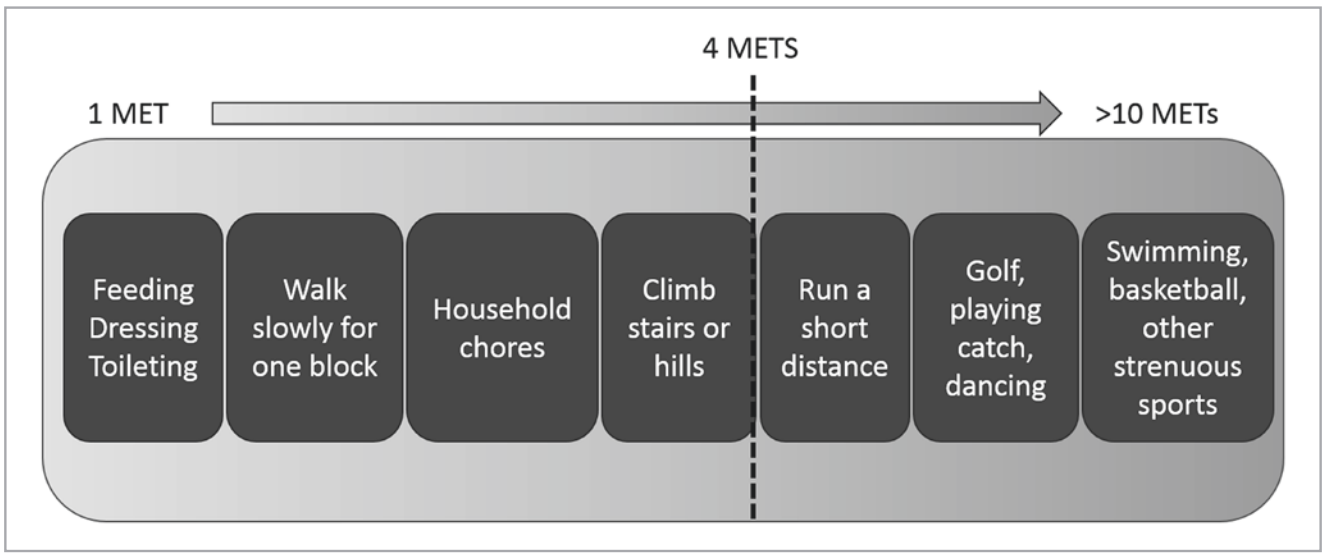

FIGURE 23-1

Functional capacity assessment

- Urgency and risk of planned surgical procedure
  - If emergency noncardiac surgery is required (e.g., death or major complications are certain or extremely likely without surgery), proceed to surgery without further cardiovascular evaluation (Class IC)
  - If noncardiac surgery is not emergent, determine perioperative cardiac risk
    - Need for further testing and treatment is dependent on overall perioperative cardiac risk (see below)

PHYSICAL EXAMINATION (TABLE 23-1)

INTEGRATED APPROACH (FIG. 23-2, FROM FLEISHER ET AL. [2])

PERIOPERATIVE RISK ESTIMATION

- Several tools exist to estimate perioperative risk of cardiac complications
  - Revised Cardiac Risk Index (RCRI)
    - Uses 6 predictors of risk for major cardiac complications (high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin-dependent diabetes, and creatinine > 2 mg/dL)
    - 0–1 predictor = low risk and ≥2 predictors = high risk
    - Strengths: Well-established and externally validated
    - Limitations: Developed in 1999, MI defined using older biomarkers, does not perform well with vascular surgeries, unclear whether generalizable to newer less invasive surgeries (e.g., laparoscopic procedures)

TABLE 23-1

PHYSICAL EXAMINATION IN PERI-OPERATIVE ASSESSMENT

EXAMINATION COMPONENT	FINDINGS THAT SHOULD PROMPT ADDITIONAL INVESTIGATION
Vital signs	Hypotension, hypertension, tachycardia, bradycardia
Carotid pulse	Bruits, abnormal pulse contour
Jugular venous pressure/pulse	Elevation or abnormal contour
Pulmonary auscultation	Crackles, wheezing; dullness to percussion suggestive of pleural effusion
Cardiac auscultation	Murmurs (particularly if loud, harsh, or associated with other findings suggestive of heart failure or other pathology), irregular rhythm
Peripheral pulses	Diminished (particularly if associated with bruits and/or limb discoloration)
Edema	If severe, unilateral, or associated with other findings of heart failure

- American College of Surgeons National Surgical Quality Improvement Program (NSQIP) myocardial infarction or cardiac arrest (MICA) calculator [10]
  - Utilizes age, serum creatinine, American Society of Anesthesiologists (ASA) classification, preoperative functional status, and procedural site to predict risk of MI or cardiac arrest
  - Found to have improved predictive value when compared to RCRI in the NSQIP national database, although has not been externally validated
  - https://qxmd.com/calculate/calculator_245/gupta-perioperative-cardiac-risk
- American College of Surgeons National Surgical Quality Improvement Program (NSQIP) universal surgical risk calculator [11]
  - A web-based tool utilizing 20 patient factors (but not necessarily cardiac factors) and the surgical procedure code
  - Predicts morbidity (both cardiovascular and non-cardiovascular) and mortality
  - http://riskcalculator.facs.org/RiskCalculator/index.jsp
- NSQIP calculators are not externally validated at present, and there is some concern these may underestimate MI, based on the registry definition of ST-segment MI or significant troponin elevation that occurred in symptomatic patients

- Current ACC/AHA guidelines seem to segregate patients into low overall perioperative risk (<1%) and elevated (cf not low) risk categories

PREOPERATIVE CARDIOVASCULAR TESTING

A) Electrocardiography (EKG)

- EKG may provide prognostic information in patients with active cardiac conditions (e.g., ischemia, arrhythmia), and a baseline for comparison in cases of suspected perioperative cardiac complication,
- However, there are no Class I indications for pre-operative EKG (with the exception of transplant candidates; see Section 10E below).
- A pre-operative EKG is reasonable in the following setting:
  - Patients with known coronary artery disease (CAD), significant arrhythmia, peripheral arterial disease, cerebrovascular disease, or other significant structural heart disease, except for those undergoing low-risk surgery (Class IIa)
- Preoperative 12-lead EKG is NOT recommended for asymptomatic patients undergoing low-risk procedures (Class III) [12]

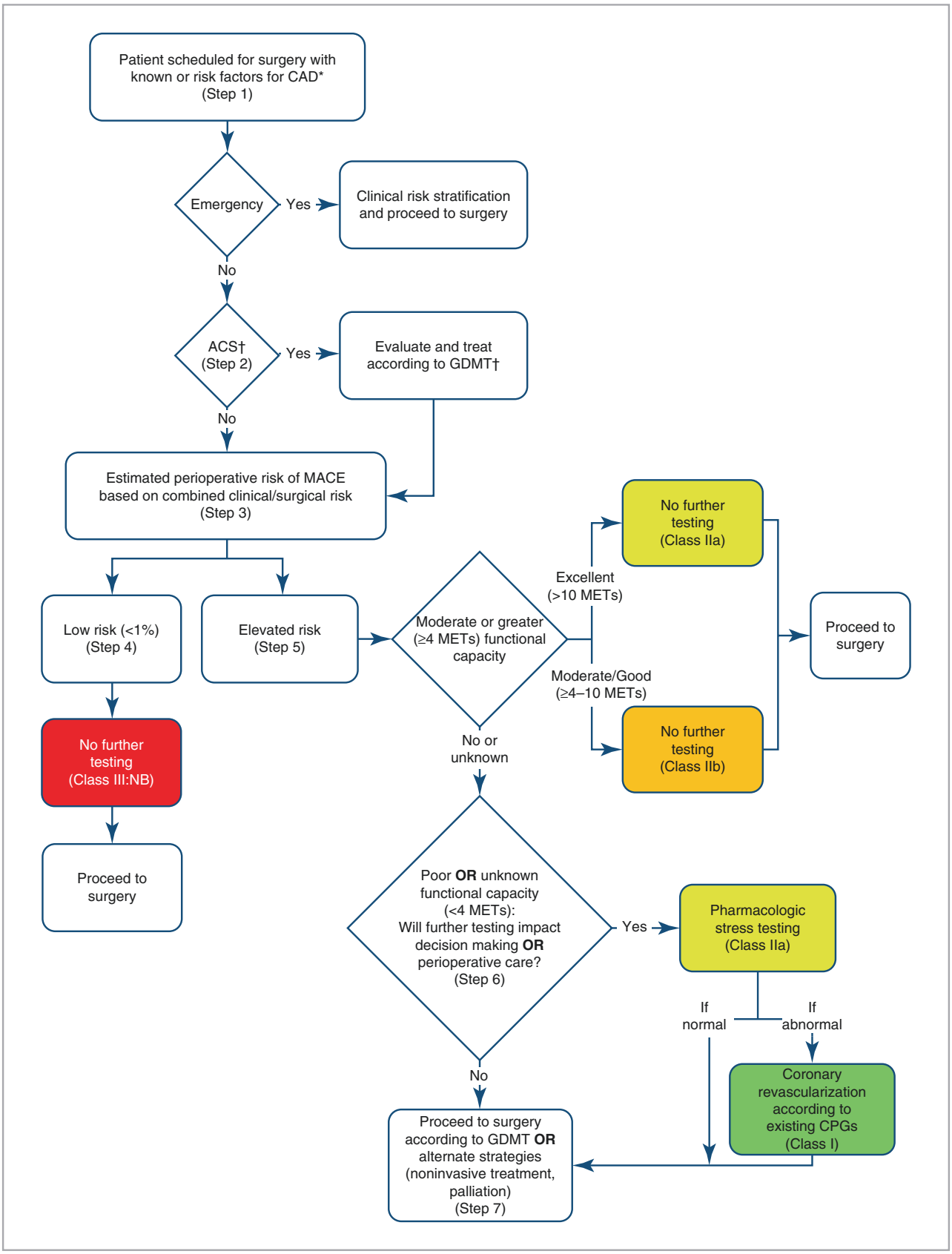

FIGURE 23-2

Integrated approach to peri-operative assessment

B) Noninvasive (Stress) Testing

- Provides an objective measure of functional capacity, identifies myocardial ischemia, and helps estimate perioperative cardiac risk and long-term prognosis
- Patients with diagnosed active cardiac issues should undergo appropriate testing and treatment, as guided by the condition (Class I)
- Noninvasive testing indicated in patients with elevated perioperative risk, stratified based on consideration of functional capacity (often measured in metabolic equivalents or "METs")
  - In patients with elevated perioperative risk and "excellent" (>10 METs) functional capacity, it is reasonable to proceed with surgery without noninvasive testing (Class IIa)
  - In patients with elevated perioperative risk and "moderate to good" (≥4–10 METs) functional capacity, may be reasonable to proceed with surgery without noninvasive testing (Class IIb)
  - In patients with elevated perioperative risk and "poor" (<4 METs) or unknown functional capacity, may be reasonable to perform noninvasive testing for ischemia, if results will change management (Class IIb)
- Noninvasive testing should NOT be performed in patients undergoing low-risk surgery (Class III)
- Exercise stress testing is generally favored over other modalities, if possible; choice of vasodilator as a stress modality, and addition of imaging, depends on local expertise and patient characteristics (e.g., imaging with abnormal resting EKG, avoidance of dobutamine in patients with ventricular arrhythmia, avoidance of adenosine in patients with bronchospasm, etc.) [13]

C) Transthoracic Echocardiography

- Provides a measure of left ventricular (LV) function, identifies and characterizes valvular disease, estimates pulmonary artery pressure
  - Indicated in the following settings:
    - Dyspnea of unknown origin (Class IIa)
    - Known heart failure with worsening dyspnea or other change in clinical status (Class IIa)
    - Preoperative evaluation is suggestive of undiagnosed heart failure
    - Clinically suspected moderate or greater degrees of valvular regurgitation or stenosis if either (1) no prior echocardiography within 1 year, or (2) a significant change in clinical status or physical examination since last evaluation (Class I) [2]
    - Liver or kidney transplantation candidate (see Section 10E below)
- Routine perioperative evaluation of LV function is NOT recommended (Class III) [14]

PERIOPERATIVE MEDICATIONS

A) Beta-blockers

- Overall benefit in reducing cardiac events is unclear
  - The DECREASE family of trials suggested significant reduction in perioperative events [15], but these trials have been discredited due to concerns regarding academic misconduct [16]

- Multiple subsequent RCTs and a large meta-analysis showed no overall benefit [17–20]
- POISE: Largest study, high risk patients undergoing intermediate-to-high risk surgery; metoprolol reduced non-fatal MI but *increased* stroke and total mortality [21]
  - POISE criticized by de novo administration of large doses of long-acting metoprolol, only 2–4 h prior to surgery
  - Post-POISE metaanalysis [22] of secure trials, namely excluding DECREASE family of trials, shows reduction in non-fatal MI with beta-blockers but increases in hypotension, stroke, and 30 day mortality.

- Nevertheless, beta blockers can have salutary effects in patients with arrhythmia (e.g., rate control) and cardiomyopathy (e.g., neurohormonal blockade).
- Guideline-based perioperative beta blocker indications:
  - Continue if already receiving beta-blockers (Class I)
  - Consider in case of intermediate or high risk preoperative testing or ≥3 RCRI risk factors (Class IIb) (eg judicious use in high risk surgeries, documented myocardial ischemia, etc.).
  - Beta blockers should NOT be started on the day of surgery (Class III)
- If starting beta blockade to prevent perioperative events, best to do so weeks in advance, and actively and carefully titrate dose based on individual heart rate and blood pressure parameters. Note that controversy remains about patient selection, optimal duration, and titration protocol.

B) Antiplatelet Agents

- Aspirin
  - POISE-2 demonstrated no benefit to starting aspirin prophylactically in patients at high risk for perioperative events, and a slightly higher risk of perioperative major bleeding [23].
  - Thus, in patients without prior coronary stenting, initiation or continuation of aspirin is not beneficial (Class III) unless risk of ischemic events outweighs risk of surgical bleeding.
  - A retrospective subgroup of POISE-2 patients who had undergone previous percutaneous coronary intervention showed that aspirin reduced a composite of death or non-fatal MI, without increase in bleeding [24].
  - Aspirin may be also continued in patients currently receiving it, when risk of increased cardiac events outweighs risk of bleeding (Class IIb).
- Thienopyridines (clopidogrel, prasugrel, ticagrelor; ADP receptor/P2Y12 blockade) (see Table 23-2)
  - Guidelines recently updated to shorten mandatory duration of dual antiplatelet (aspirin + thienopyridine) therapy after stent implantation given recent data demonstrating lower in-stent thrombosis rates with the newest generation of drug eluting stents [25, 26]
  - For elective surgeries requiring interruption of DAPT, surgery should be postponed until:
    - 2 weeks after percutaneous balloon angioplasty;
    - 30 days after bare metal stent deployment; and
    - 6 months after drug eluting stent deployment (Class I) [27]
  - Elective surgery requiring interruption of DAPT may be considered at 3 months after drug eluting stent deployment, if the risk of further delay of surgery is greater than the expected risks of stent thrombosis (Class IIb) [28]
  - For urgent noncardiac surgeries, DAPT should be continued during the first 4–6 weeks after BMS or DES implantation, unless the risk of bleeding outweighs the benefit of stent thrombosis protection (Class I)

TABLE 23-2

DURATION OF MANDATORY DUAL ANTIPLATELET THERAPY AFTER PERCUTANEOUS CORONARY INTERVENTION

TYPE OF INTERVENTION/ STENT	DURATION OF MANDATORY DUAL ANTIPLATELET THERAPY
Balloon angioplasty	2 weeks
Bare metal stent	30 days
Drug eluting stent	6 months[a]

[A]consider 3 Months if Risk of Further Delay in Surgery Outweighs Risk of Stent Thrombosis

C) Anticoagulation

- Whether to simply discontinue therapeutic anticoagulation in patients with an existing indication prior to surgery versus provide bridging therapy with low molecular weight heparin or unfractionated heparin depends on balance of bleeding and thrombotic risk [28, 29]
  - Bridging should usually be provided in patients with high risk of thromboembolism (e.g., atrial fibrillation with $CHADS_2$ score of 5–6; mechanical mitral valve; mechanical aortic valve with a thromboembolic risk factor such as recent stroke, venous thromboembolism within 3 months, or significant thrombophilia)
  - Bridging is generally not required in patients with low risk of thromboembolism (e.g., atrial fibrillation with $CHADS_2$ score 0–2, mechanical aortic valve with no thromboembolic risk factors, venous thromboembolism ≥1 year)
  - The cardiologist must decide to bridge on a case-by-case basis in patients at intermediate risks of thromboembolism (e.g., mechanical aortic valve with thromboembolic risk factors, venous thromboembolism within 3–12 months, mild-moderate thrombophilia)
    - BRIDGE trial demonstrated that AF patients at intermediate stroke risk (including CHADS2 scores of 3–4) likely do not benefit from routine bridging [30]
- Discontinuation of anticoagulants: elective surgery
  - Warfarin should be discontinued at least 5 days before surgery and the international normalized ratio (INR) should be monitored before surgery
  - Direct-acting oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban, edoxaban), are often discontinued generally 48–72 h before surgery (timing depends on bleeding risk of surgery, antiplatelet agents, patient's age and renal function both of which may impact clearance) [31]
- Reversal of anticoagulants: urgent/emergent surgery
  - Warfarin: reversal with prothrombin complex concentrate or fresh frozen plasma (acutely) and/or vitamin K (subacutely)
  - Direct-acting oral anticoagulants: reversal with idarucizumab (dabigatran) or andexanet alfa (rivaroxaban, apixaban, edoxaban). Prothrombin complex concentrate can be given if above not available.
- Postoperative resumption of anticoagulation depending on postsurgical bleeding risk of spinal epidural hematomas
  - There are more stringent concerns for resumption after neuraxial anesthesia due to the risk of spinal epidural hematoma. Safety of resuming anticoagulation may depend on difficulty of the neuraxial procedure, so consider discussing timing with anesthesia and surgery [32].

D) Statins

- Associated with significant reduction in perioperative cardiac events, with magnitude of benefit likely greatest in high-risk patients [33, 34]
  - Benefit may extend to patients not previously on statins [35], but data are retrospective or from small trials
- Should be continued in patients already taking statins (Class I)
- Perioperative initiation is reasonable in patients undergoing vascular surgery (Class IIa)

E) Angiotensin converting enzyme (ACE)-inhibitors/Angiotensin II receptor blockers (ARB)

- Should be continued in patients already taking these agents, unless prohibited by hypotension (Class IIa)
- Caution is advised when epidural anesthesia is used due to potential for profound hypotension, as well as other circumstances where hypotension is anticipated

CORONARY REVASCULARIZATION

A) Indications are same as if patient were not going to surgery, i.e.:

- Stable angina with significant left main coronary stenosis (Class I)
- Stable angina with 3-vessel disease (Class I)
- Stable angina with 2-vessel disease with significant proximal left anterior descending (LAD) stenosis and either left ventricular ejection fraction (LVEF) <50% or ischemia on noninvasive testing (Class I)
- Patients with high-risk unstable angina, non-ST elevation MI, or ST-elevation MI (Class I)
- In observational studies, patients with recent revascularization for standard indications (i.e., not only the perioperative state), reduces risk for subsequent surgery [36, 37]

B) Coronary revascularization is NOT indicated for:

- Routine prophylactic revascularization in patients with stable CAD (Class III)
  - Increased risk of in-stent thrombosis when surgery is performed in the immediate post-percutaneous coronary intervention (PCI) period [38, 39]
  - CARP trial demonstrated no immediate or long-term benefit to revascularization for stable CAD (>70% stenosis of at least one coronary artery) [40]. Remember, CARP was a treatment trial, not a screening trial, and CARP specifically excluded left main disease, severe aortic stenosis, and severe LV systolic dysfunction from its patient population.

SPECIAL TOPICS

A) Arrhythmia

- Supraventricular Arrhythmia
  - In stable supraventricular arrhythmia, generally utilize a rate-control strategy with digoxin, beta-blockers or calcium channel blockers
  - Rhythm control (including cardioversion) in selected patients with hemodynamic instability or difficulty with rate control

- Nonsustained Ventricular Arrhythmia
  - Routine therapy not indicated in the absence of symptomatic or sustained arrhythmia, hemodynamic compromise or ongoing ischemia
  - Consider assessment of LVEF
  - Typically initiate beta blockade, followed by anti-arrhythmic drugs (e.g., amiodarone or lidocaine) if persistent

B) Implantable cardioverter defibrillators (ICD) and pacemakers

- Routine preoperative pacemaker implantation not indicated in the absence of standard indications
- Electrocautery may interfere with devices, leading to:
  - Device reset to default mode
  - Inhibition of pacemaker output
  - Oversensing leading to either inappropriate pacing or lack of pacing
  - Inappropriate ICD firing
  - Myocardial injury with lead failure
- Recommendations
  - Devices should be evaluated and interrogated preoperatively
  - Pacemakers should be reprogrammed to asynchronous mode or a magnet should be placed over the device during surgery to maintain VOO mode
  - For ICDs, tachyarrhythmia algorithms should be deactivated during surgery, with reactivation postoperatively
  - Bipolar electrocautery should be employed, and its use minimized
  - The distance between electrocautery and implanted device should be maximizedb

C) Heart Failure and Cardiomyopathy

- Judicious use of intra- and post-operative intravenous fluids
- Diuresis to maintain euvolemic state
- Continued use or early resumption of afterload reduction and beta blockade when hemodynamically stable
  - Particular caution is advised with re-initiation of vasodilators when epidural anesthesia is used
- Consider preoperative placement of pulmonary artery catheter in patients with severe heart failure expected to significantly affect hemodynamics perioperatively (Class IIb)

D) Valvular Heart Disease

- In patients with standard indications for valvular intervention on the basis of symptoms and severity of valvular disease, valvular intervention prior to elective surgery is effective in reducing perioperative risk (Class I)
- Elevated-risk elective noncardiac surgery is reasonable to consider with the following valvular lesions, as long as the patient is asymptomatic [2, 41]:
  - Severe aortic stenosis (Class IIa)
  - Severe aortic regurgitation with normal LVEF (Class IIa)
  - Severe mitral regurgitation (Class IIa)
  - Severe mitral stenosis, if valve morphology is not favorable for percutaneous mitral balloon commissurotomy (Class IIb)
- Intraoperative and postoperative hemodynamic monitoring is likely necessary for patients in these scenarios (this likely supersedes the ACC/AHA general recommendation that pulmonary artery catheters may be considered for medical conditions that "significantly affect hemodynamics") (Class IIb)
- Although rarely performed, in patients with symptomatic severe aortic and/or mitral stenosis, percutaneous catheter balloon valvulotomy may be considered as a bridge

E) Liver and Kidney Transplantation

- Given special circumstances surrounding liver and kidney transplantation, specific considerations are given with regard to perioperative cardiac risk in this population.
  - Solid organs are rare, candidates are frequently advanced in age, and transplantation procedures are often accompanied by significant fluid shifts and hemodynamic stressors
  - Incidence of MI 8.7–16.7% by 3 years after kidney transplant listing and 4.7–11.1% after kidney transplant [42]
  - Cardiovascular diseases in aggregate are the most common cause of death at all times after kidney transplantation, with highest rates in the peri-transplantation period
- Recommendations from ACC/AHA Scientific Statement 2012 (kidney transplantation) [43]
  - A preoperative 12-lead EKG is recommended for potential kidney transplantation candidates with known coronary heart disease, peripheral arterial disease, or cardiovascular symptoms (Class I)
  - It is reasonable to obtain echocardiography in potential kidney transplantation candidates to assess LV function and valvular function (Class IIa)
  - Noninvasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions if ≥3 risk factors are present (diabetes, prior cardiovascular disease, dialysis for >1 year, left ventricular hypertrophy, age >60, smoking, hypertension, dyslipidemia) (Class IIb)
  - The usefulness of periodic screening for myocardial ischemia in kidney transplantation candidates is uncertain (Class IIb)
- Recommendations from ACC/AHA Scientific Statement 2012 (liver transplantation) [38]
  - It is reasonable to obtain echocardiography in potential liver transplantation candidates to assess for pulmonary hypertension and/or intrapulmonary shunt in liver transplantation candidates (Class IIa)
  - Noninvasive stress testing may be considered in liver transplantation candidates with no active cardiac conditions if ≥3 risk factors are present (diabetes, prior cardiovascular disease, dialysis for >1 year, LV hypertrophy, age >60, smoking, hypertension, dyslipidemia) (Class IIb)

POSTOPERATIVE MANAGEMENT

A) MI surveillance

- EKG
  - An EKG should be performed in the setting of signs or symptoms suggestive of myocardial ischemia, MI, or arrhythmia (Class I)
  - Routine post-operative screening EKGs in patients at high risk for perioperative MI, but without signs or symptoms suggestive of myocardial ischemia, MI, or arrhythmia, are of uncertain benefit (Class IIb)
- Troponin measurement
  - Recommended in the setting of signs or symptoms suggestive of myocardial ischemia or MI (Class I)
  - Routine post-operative troponins in patients at high risk for perioperative MI but without signs or symptoms suggestive of myocardial ischemia, MI, or arrhythmia are of uncertain benefit (Class IIb)

- NOT indicated in asymptomatic patients not at high risk for perioperative MI (Class III)
- There is limited data on high-sensitivity troponin

B) Arrhythmia

- Standard diagnostic algorithms apply
- Treatment directed at underlying cause
- Electrolyte, acid/base, and volume abnormalities are more common in immediate postoperative period and may be associated with arrhythmia

Questions and Answers

Questions

1. You are asked to consult on a 75-year-old woman with a past medical history of hypothyroidism and hypertension who is now presenting with a hip fracture and will be taken to the operating room for urgent open reduction and internal fixation. At baseline, she has no dyspnea or chest pain and walks two city blocks to the grocery store several times a week. Her blood pressure is 125/70 mm Hg and the heart rate is 75 beats per min. Cardiovascular auscultation discloses a soft, non-radiating, II/VI systolic ejection murmur at the base. Her medications include levothyroxine and hydrochlorothiazide. Laboratory studies are notable for an LDL of 110 mg/dL, HDL 55 mg/dL. What is the next step?

a) Initiate metoprolol.
b) Initiate atorvastatin.
c) Order an echocardiogram.
d) Order a pharmacologic stress test.
e) Allow her to proceed to surgery without any additional interventions.

2. You are asked to consult on a 66-year-old man with a history of CAD, hypertension, hyperlipidemia, and ischemic cardiomyopathy with a LVEF of 30% who has been newly diagnosed with PAD after ankle-brachial indices were performed due to claudication with exertion. He is scheduled to undergo femoral-popliteal bypass surgery. He underwent cardiac catheterization for a non-ST elevation MI 9 months ago, with implantation of a drug-eluting stent. His medications include carvedilol, losartan, pravastatin, furosemide, clopidogrel, and aspirin. On physical examination, he appears euvolemic without lower extremity edema and warm extremities, has a regular rate and rhythm without murmurs, and has an ICD. He does not have any angina and can walk up a flight of stairs, but his activity is limited beyond that due to lower extremity pain. Laboratory studies are notable for HDL 40 mg/dL and LDL 130 mg/dL. What do you recommend?

a) Order a pharmacologic stress test.
b) Order an exercise stress test with perfusion imaging.
c) Delay surgery for at least 3 months.
d) Delay surgery for at least 6 months.
e) Allow him to proceed to surgery without any additional interventions.

3. The above patient's surgery is delayed due to a death in the family, and he returns to your office 3 months later (one year after stent placement) requesting "clearance" for surgery next month. What is the most important modification to make in the immediate preoperative period?

a) Discontinue aspirin.
b) Discontinue clopidogrel.
c) Discontinue losartan.
d) Intensify statin therapy.
e) Turn off his ICD.

Answers

1. Answer: E. Allow her to proceed to surgery without additional interventions. This patient has one risk factor for coronary artery disease (hypertension). However, her hip fracture surgery is urgent, and she is able to routinely perform activities approximately 4 METs. Therefore, additional testing is not indicated, especially since it may delay her needed surgery. Initiation of perioperative metoprolol is not likely to be beneficial and may even cause harm given lack of adequate time to allow for careful initiation and titration of therapy (ideally several days to weeks). Statins may be beneficial in high-risk patients, and should be continued in patients who are already taking this class of medication, but there is no convincing evidence that this relatively low-risk patient would benefit.

2. Answer: E. Allow him to proceed to surgery without any additional interventions. This patient has recently revascularized CAD without evidence of ongoing ischemia; therefore, there is no indication for additional testing. He is on an appropriate medical regimen, his heart failure is well-compensated, he has sufficient functional status, and an ICD has (appropriately) been placed. Elective surgery requiring interruption of DAPT after PCI utilizing drug-eluting stents should optimally be delayed at least 6 months. This patient's drug eluting stent was placed 9 months ago, so the benefit of surgery likely outweighs the risk of briefly interrupting his P2Y12 inhibitor at this juncture.

3. Answer: B. Discontinue clopidogrel. Since more than a full year has elapsed since stenting was performed, clopidogrel can be safely discontinued, thereby reducing the patient's bleeding risk during surgery. In patients with indications for aspirin, it should not be routinely discontinued prior to surgery. ACE inhibitors and ARBs are typically discontinued the day of surgery, but there is no need to discontinue losartan a month before surgery. The patient's LDL is not at goal for a patient with known coronary artery disease, but intensifying statin therapy is less important than discontinuing clopidogrel in the preoperative period. The patient's device should be interrogated and tachyarrhythmia treatment algorithms should be turned off on the day of surgery.

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CHAPTER 24

NASRIEN E. IBRAHIM AND JAMES L. JANUZZI JR.

Diagnosis and Management of Acute Heart Failure

CHAPTER OUTLINE

ABBREVIATIONS

ACC	American College of Cardiology
ACEi	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndromes
ADHF	Acute decompensated heart failure
AHA	American Heart Association
AR	Aortic regurgitation
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
Ca	Calcium
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
Cr	Creatinine
CRT	Cardiac resynchronization therapy
CVA	Cerebrovascular accident
CXR	Chest X-ray
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
ICD	Implantable cardioverter defibrillator
JVP	Jugular venous pressure
K	Potassium
LFT	Liver function tests
LV	Left ventricle
LVEF	Left ventricle ejection fraction
MCS	Mechanical circulatory support
Mg	Magnesium
Na	Sodium
NSAIDs	Nonsteroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association

PAD	Peripheral arterial disease
PCWP	Pulmonary capillary wedge pressure
PDE	Phosphodiesterase
PVC	Premature ventricular contractions
PVR	Pulmonary vascular resistance
RV	Right ventricle
SVR	Systemic vascular resistance
TIA	Transient ischemic attack
VAD	Ventricular assist device
VT	Ventricular tachycardia

EPIDEMIOLOGY [1]

- 670,000 people are diagnosed with HF annually in the US; about half of people who develop HF die within 5 years of diagnosis; more than 290,000 deaths are associated with HF
- HF costs the United States an estimated $30.7 billion each year
- HF is the most common reason for hospitalization in people over age 65
- Over one million hospitalizations occur annually due to acute HF
  - More than 70% of admissions are from worsening of chronic HF (i.e. acute on chronic HF)
    - In-hospital mortality is 4% and 1 year mortality is 20% [2]
    - 30-day readmission rate is high
      - Readmission rates of 26.9% for HF versus 19.1% for all comers [3]
- Based on acute HF registries (The Acute Decompensated Heart Failure National Registry [ADHERE] [2], Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure [OPTIMIZE-HF] [4], EuroHeart Failure Survey II [EHFS II] [5]), most who are admitted with HF are over age 70, have a prior history of admission for HF, and 40–52% have HFpEF

PATHOPHYSIOLOGY

A variety of mechanisms contribute to developing acute HF and they consist of an underlying substrate, a triggering mechanism, and perpetuating factors [6]. Regardless of the substrate, trigger, or perpetuating factor(s), a unifying theme in acute HF is the presence of volume overload/congestion.

A) **Substrate: myocardial structure and function**

- Normal myocardial substrate that has suffered an acute injury that could be completely reversible, partially reversible, or irreversible
  - Most common cause: myocardial ischemia/infarction
  - Inflammation (myocarditis, autoimmune)
  - Stress cardiomyopathy
- Abnormal underlying substrate
  - American College of Cardiology (ACC)/American Heart Association (AHA) Stage B HF with first symptomatic event
  - Those with chronic compensated HF who present with an acute decompensation event
    - Most common presentation

B) Triggering mechanisms

- Acute coronary syndromes (ACS)/ischemia
- Medication non-adherence, iatrogenic changes in medications, drug-drug interactions
- Dietary indiscretion
- Worsening renal dysfunction
  - Renal artery stenosis [7], so-called "Pickering Syndrome"
- Arrhythmias (atrial or ventricular)
  - Atrial fibrillation [8]
  - Premature ventricular contractions (PVC) [9]
  - Ventricular tachycardia (VT)
- Pulmonary embolism
- Infections
- Severe hypertension
- Iatrogenic volume administration (e.g. intravenous fluids or blood transfusion)
- Cardiotoxic agents
  - Antineoplastic agents
    - *Anthracyclines*
      - Doxorubicin
      - Daunorubicin
      - Epirubicin
      - Idarubicin
    - *Anthraquinolones*
      - Mitoxantrones
    - *Alkylating agents*
      - Busulfan
      - Cisplatin
      - Cyclophosphamide
      - Ifosfamide
    - *Antimetabolites*
      - 5-Fluorouracil
    - *Antimicrotubules*
      - Paclitaxel
      - Vinca alkaloids
        - Vi*ncristine*
        - *Vin*blastine
    - *Tyrosine-kinase inhibitors*
      - Bevacizumab
      - Imatinib
      - Lapatinib
      - Sunitinib
      - Sorafenib
      - Trastuzumab
    - *Hormone-modifying therapy*
      - Androgen-deprivation

- Aromatase inhibitors
- *Miscellaneous*
  - All-trans retinoic acid
  - Arsenic trioxide
  - Pentostatin
- Cocaine
- Alcohol
- Ephedra

- Medications
  - Corticosteroids
  - Negative inotropes (e.g. verapamil, diltiazem)
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
- RV apical pacing [10]
- Hyper/hypothyroidism
- Systemic inflammation, including infections such as influenza [11]
- Sleep apnea

C) **Perpetuating factors lead to chronic HF (see Chap. 25)**

CLASSIFICATION

Two major classification systems have been described for patients with HF [12]

A) New York Heart Association (NYHA) functional classification of HF symptoms (Table 24-1)
B) ACC/AHA staging system for HF (Table 24-2)

TABLE 24-1

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION OF HEART FAILURE SYMPTOMS

Class I	No symptoms with ordinary activity
Class II	Slight limitation of physical activity; comfortable at rest, but **ordinary physical activity** results in fatigue, dyspnea or angina
Class III	Marked limitation of physical activity; comfortable at rest, **but less than ordinary physical activity** results in fatigue, dyspnea or angina
Class IV	Unable to carry out **any physical activity** without symptoms. Symptoms may be present at rest

TABLE 24-2

AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION STAGING SYSTEM FOR HEART FAILURE

Stage A	High risk for developing HF	Hypertension Coronary artery disease Diabetes mellitus Family history of cardiomyopathy
Stage B	Asymptomatic HF	Previous myocardial infarction Left ventricular systolic dysfunction Asymptomatic valvular disease
Stage C	Symptomatic HF	Known structural heart disease Shortness of breath and fatigue Reduced exercise tolerance
Stage D	Refractory end-stage HF	Marked symptoms at rest despite maximal medical therapy

HF heart failure

TABLE 24-3

ESTIMATION OF HEMODYNAMIC PROFILE BASED ON EXAM FINDINGS

Congestion
■ S3 and/or S4 gallop
■ Prominent P2
■ Elevated JVP (JVD >10 cm corresponds to PCWP >22 mmHg, with 80% accuracy)
■ Hepatojugular reflux
■ Hepatomegaly
■ Edema
■ Pulsatile liver
■ Ascites
■ Rales or wheezes
Low Cardiac Output
■ Narrow pulse pressure (usually less than 25 mmHg)
■ Cool extremities
■ Lethargy/altered mentation
■ Hypotension
■ Sinus tachycardia
■ Pulsus alternans

JVP jugular venous pressure, *JVD* jugular venous distention, *PCWP* pulmonary capillary wedge pressure

INITIAL ASSESSMENT

Presentation

a). Dyspnea on exertion

- Most **sensitive** symptom

b). Paroxysmal nocturnal dyspnea

- Most **specific** symptom [13]

c). Peripheral edema

- Relatively common (66%), but only present in those with right sided HF

d). Fatigue
e). Cough, particularly nocturnal
f). Chest discomfort

Physical Examination [14]

A rapid initial assessment should be performed to identify (Table 24-3):

- Presence of congestion
- Presence of low output/cardiogenic shock
- Presence of co-morbidities and precipitating factors
  - *Note: clinical evaluation is often inaccurate*

Diagnostic Evaluation (Table 24-4)

1. Chest X-ray (CXR)
   - Initial radiographs may not show evidence of pulmonary congestion [15]
   - >25% of patients with acute HF present without CXR findings [16]
   - CXR findings include:
     - Dilated upper lobe vessels
     - Interstitial edema

TABLE 24-4

POSSIBLE ETIOLOGIES OF ACUTE HEART FAILURE

Cardiac causes	■ Progression of underlying cardiomyopathy ■ New onset/acute cardiomyopathy – Postpartum cardiomyopathy – Myocarditis – Takotsubo cardiomyopathy ■ Ischemia ■ Arrhythmias ■ Pericardial – Constriction – Tamponade ■ Valvular dysfunction – Stenosis – Regurgitation
Pressure overload	■ Severe hypertension
Volume overload	■ Renal dysfunction ■ Sodium/volume load ■ Medication non-adherence
High output	■ Thyroid disease ■ Shunts – Intracardiac – Extracardiac (A-V fistula) ■ Anemia ■ Sepsis
Miscellaneous causes	■ Infection ■ Pulmonary embolism ■ New medications/substances – NSAIDs – Corticosteroids – Cardiotoxic agents

NSAIDs nonsteroidal anti-inflammatory drugs

- Enlarged pulmonary arteries
- Pleural effusions
- Alveolar edema
- Prominent superior vena cava
- Kerley B lines

2. Electrocardiogram
   - Assess for [17]
     - Acute myocardial ischemia/infarction
     - LV hypertrophy
     - Arrhythmias
       - Atrial fibrillation
         - Present in 31% of patients presenting with acute HF
       - Heart block
       - PVC
     - Pacemaker malfunction, particularly in those patients with cardiac resynchronization therapy (CRT) devices assess for adequate biventricular pacing
3. Laboratory tests
   - Electrolytes, including sodium (Na), calcium (Ca), potassium (K), and magnesium (Mg)

- Renal function (blood urea nitrogen [BUN], Creatinine [Cr])
- Liver function tests (LFT)
- Thyroid function tests
- Complete blood count (CBC)
- Natriuretic peptides
  - Two forms have been studied and are the gold standard HF biomarkers:
    - B-type natriuretic peptide (BNP) and its precursor N-terminal proBNP (NT-proBNP)
  - Can be used when the diagnosis of acute HF is uncertain and for prognostication [12]
    - In those with acute HF, marked elevation in BNP or NT-proBNP at presentation is prognostic for in-hospital death. A BNP or NT-proBNP after HF treatment provides incremental information regarding risk for post-discharge events
  - An elevated BNP or NT-proBNP is not sufficient to make a diagnosis of acute HF, as concentrations may be elevated in states other than acute HF, including chronic, compensated HF, acute myocardial infarction, valvular heart disease, and arrhythmias; non-cardiac causes include advanced age, sepsis, and renal failure
  - A low BNP or NT-proBNP has high negative predictive value to exclude HF
    - Falsely low BNP or NT-proBNP may be seen in obesity, HFpEF, or HF involving the RV more than the LV
- Troponins
  - As coronary ischemia is an important cause of de novo HF as well as decompensation of previously stable HF, troponin should always be measured in those presenting with acute HF
  - An elevated troponin may be seen in those with acute HF in the absence of coronary ischemia, however, so correlation with the entire clinical picture is advised
  - Elevated troponin in HF is associated with worse outcome, regardless of presence of acute MI

4. Echocardiography
   - Assess LV and RV Function
     1. Preserved or reduced
     2. Ventricular structure
     3. Size
     4. Wall thickness
   - Other structural abnormalities
     5. Valvular
     6. Pericardial
     7. Atrial size
5. Cardiac catheterization [12]
   - Routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute HF
   - When ischemia may be contributing to HF, coronary arteriography is reasonable
   - Monitoring with a pulmonary artery catheter should be performed in patients with respiratory distress or impaired systemic perfusion when clinical assessment is inadequate
   - Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF with persistent symptoms and/or when hemodynamics are uncertain (for example, in a patient who is volume-overloaded by clinical exam but renal function continues to worsen with diuretic use)

6. Endomyocardial biopsy [12]
   - Should not be performed in the routine evaluation of patients with HF
   - Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy (for example, in a patient presenting with incessant VT and hemodynamic collapse and a diagnosis of Giant Cell Myocarditis is suspected)

INDICATIONS FOR HOSPITALIZATION

A) According to the Heart Failure Society of America (HFSA) guidelines [12], hospitalization is recommended for patients with acute HF who present with the following clinical circumstances:
   - Hypotension
   - Worsening renal function
   - Altered mentation
   - Rest dyspnea
   - Tachypnea
   - Hypoxia
   - Hemodynamically significant arrhythmias
   - New onset rapid atrial fibrillation
   - ACS

B) Consideration of hospitalization should be made if:
   - Evidence of worsening pulmonary or systemic congestion (even in the absence of dyspnea or weight gain)
   - Marked electrolyte disturbances
   - Multiple implantable cardioverter defibrillator (ICD) firings
   - Co-morbid conditions
     - Pneumonia
     - Diabetic ketoacidosis
     - Pulmonary embolus
     - Transient ischemic attack (TIA)/cerebrovascular accident (CVA)

INITIAL MANAGEMENT OF ACUTE HF SYNDROMES

Goals

- Rapidly relieve symptoms of congestion
- Identify reversible causes, particularly ischemia
- Restore hemodynamics
- Ensure adequate oxygenation
- Prevent end organ damage
- Identify patients with low output states

Management Should Be Based on Hemodynamic Profile

- Rapid assessment and initiation of therapy can be made using the following 2 × 2 diagram demonstrating the various hemodynamic profiles of patients presenting with acute HF (Fig. 24-1) [18]

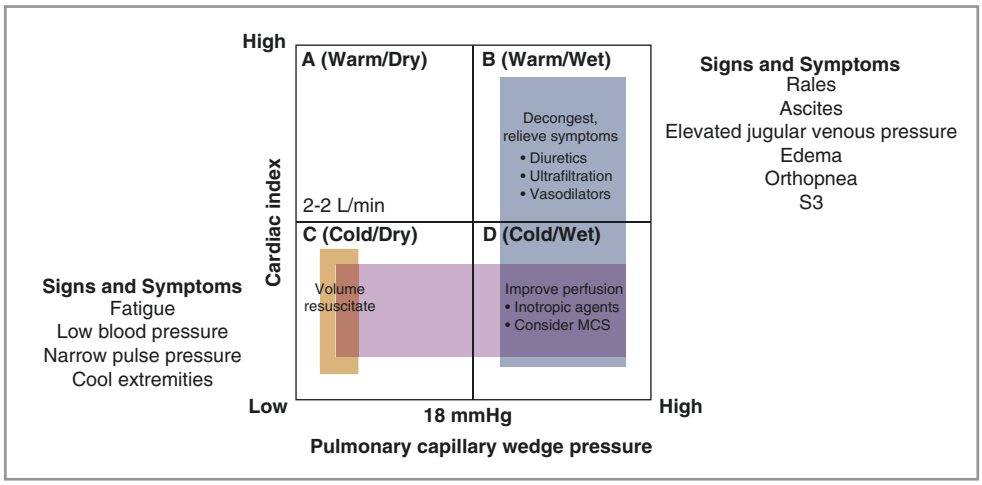

FIGURE 24-1

2 × 2 heart failure hemodynamic profiles. The diagram demonstrates the hemodynamic profiles, signs and symptoms and treatment approach of patients presenting with heart failure. Quadrant A represents the patient who is not congested and has adequate perfusion. Quadrant B represents the patient who is congested but has adequate perfusion. Quadrant C represents the patient who is congested and has poor perfusion. Quadrant D represents the patient who has a normal to low volume status and poor perfusion. Treatment approaches overlap in the low output profiles, as those patients who are congested and poorly perfused may need separate treatment approaches to both conditions. *MCS* mechanical circulatory support

After Admission

Practice guidelines recommend that the following parameters be monitored in patients hospitalized for acute HF [19]:

- Daily weight
- Daily measurement of fluid intake and output
- Vital signs (more than once daily, as indicated)
- Physical exams signs (at least daily)
  - Increased jugular venous pressure (JVP)
  - Hepatojugular reflux
  - Rales
  - Edema
  - Hepatomegaly
  - Liver tenderness
- Labs (at least daily)
  - Electrolytes
  - Renal function
- Symptom assessment (at least daily)
  - Fatigue
  - Dyspnea
  - Orthopnea
  - Paroxysmal nocturnal dyspnea or cough

Hemodynamic Monitoring (See Above)

- Studies, such as the evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness (ESCAPE) study, assessing the use of routine invasive monitoring such as pulmonary artery catheter have been essentially neutral [20]

- The routine use invasive hemodynamic monitoring is not recommended, but should be considered under the following circumstances:
  - In patients refractory to initial therapy
  - When volume status and cardiac filling pressures are unclear
  - When there is clinically significant hypotension, typically:
    - SBP <80 mmHg
    - Worsening renal function during therapy

Management of Congestion

Diuretics Are First Line Therapy in the Management of Patients with Congestion

- **Initial management consists of IV diuresis using loop diuretics** [21] **at intervals of twice to three times daily, and in some cases, continuous IV infusion**
  - Typically, **2–2.5×** home daily diuretic dose
    - For example, in a patient taking 80 mg oral furosemide daily, begin with 200 mg PO equivalent IV dosing—bumetanide 5 mg IV or furosemide 100 mg IV (1 mg of bumetanide = 20 mg of torsemide = 40 mg furosemide, roughly)
    - A response should occur within 30 min of administration
    - Diuretic dose should be escalated until desired effect occurs
    - Always watch out for electrolyte depletion (especially K and Mg) with aggressive diuresis
    - Furosemide
      - PO has an onset of 20–30 min, peak of 1–2 h and duration of 6–8 h (50% bioavailable)
      - IV has an onset of 5 min, peak of 30 min, and duration of 2 h (100% bioavailable)
  - Bolus versus continuous infusion administration of loop diuretics have similar outcomes [22]
  - Thiazide diuretics (e.g. chlorothiazide or metolazone) can be added when there is suboptimal response to loop diuretics, as they:
    - Block reabsorption of distal tubule Na
    - Antagonize renal adaptation to chronic loop diuretic treatment
    - Improve diuretic resistance with rebound Na retention
  - Caution should be exercised with aggressive diuresis, including sequential nephron blockade, as this may augment hypotensive effects of angiotensin converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB)/angiotensin receptor-neprilysin-inhibitors (ARNI)

Ultrafiltration

- Consider use in patients who are refractory to IV diuretics [23]
- Uses a small extracorporeal circuit connected to the patient via peripheral or central venous access
- Patients with hypotension may not tolerate ultrafiltration
- The Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated CHF (UNLOAD) trial [24] compared ultrafiltration to conventional diuretic therapy
  - At 48 h, compared to diuretics, ultrafiltration produced:
    - A greater reduction in weight
    - Greater fluid loss
    - Similar changes in serum creatinine

Non-invasive Positive Pressure Ventilation

- Can be considered in patients with pulmonary edema and severe dyspnea
- Improves dyspnea
- Probably has no impact on mortality or rate of intubation [25]

Vasodilator Therapy (Nitroglycerin, Nitroprusside, Nesiritide)

- Recommended for rapid symptom relief in those with pulmonary congestion or hypertension
- Use when symptoms persist despite aggressive diuretic and standard oral regimens
- Do not use if the patient has symptomatic hypotension

Nitroglycerin

- Provides venodilation, and thus reduces preload
- May reduce coronary ischemia
- At higher doses, provides reduction in systemic afterload
- Tachyphylaxis can occur
- Contraindicated in patients using phosphodiesterase (PDE)-5 inhibitors such as sildenafil

Nitroprusside

- Indicated when a marked reduction in afterload is desired
  - Hypertensive emergency
  - Severe mitral regurgitation
  - Severe aortic insufficiency
  - Acute ventricular septal rupture
  - Cardiogenic shock due to LV failure
- Potent vasodilation, equal venodilation, and arterial dilation
- Accumulation of the metabolites cyanide and thiocyanate may occur and in rare cases can be lethal; drug should only be administered for a limited period (24–48 h)
  - Thiocyanate is life-threatening when levels reach ~200 mg/L. Routine monitoring of plasma thiocyanate levels is recommended in patients with normal renal function when cumulative sodium nitroprusside doses exceed 7 mg/kg/day
- Use caution if renal or hepatic impairment
- May trigger reflex tachycardia
- Rebound vasoconstriction can occur upon discontinuation

Nesiritide

- Recombinant form of human BNP
- Reduces pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR)
- Increases cardiac output at higher doses
- Inconsistent effects on urine output, with some studies showing an increase and others with no effect [26]
- The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial [27] showed no difference in death or rehospitalization but more hypotension from nesiritide use

Support Hemodynamics

Inotropic Therapy (Table 24-5)

Vasodilating inotropes: milrinone, dobutamine
Vasopressor inotropes: dopamine, norepinephrine

- Consider use in patients who are non-responsive to or intolerant of vasodilators and diuretics
- No evidence that inotropic agents benefit patients without evidence of poor perfusion
- Short term therapy using inotropic agents has been associated with significantly higher in hospital mortality than vasodilator therapy [28, 29]

TABLE 24-5

COMPARISON OF VARIOUS VASODILATORS AND INOTROPIC AGENTS USED FOR ACUTE HEART FAILURE

MEDICATION (USUAL DOSE)	MECHANISM OF ACTION	PERIPHERAL VASODILATION	PERIPHERAL VASOCONSTRICTION	INOTROPY	CHRONOTROPY	PULMONARY VASODILATION	ARRHYTHMOGENIC
Nitroglycerin (5–10 μg/min, max 200 μg/min)	Stimulated cGMP production through activation of guanylyl cyclase	+	–	–	–	+	–
Nitroprusside (0.3–3 μg/kg/min, max 10 μ/kg/min)	Interacts with oxyhemoglobin, forming methemoglobin leading to cyanide ion and NO release	++	–	–	–	+	–
Nesiritide (0.01–0.03 μg/kg/min)	Recombinant BNP, binds to guanylate cyclase receptor, leading to increased cGMP	+	–	–	–	+	–
Milrinone (0.375–0.75 μg/kg/min)	Inhibits phosphodiesterase III	++	–	+	–	+	+
Dobutamine (2.0–20 μg/kg/min, max 40 μg/kg/min)	Stimulates β1 andβ2 receptors	+	–	+	+	–	+
Dopamine (2.0–20 μg/kg/min, max 50 μg/kg/min)	Dose dependent activation of D1, β1, and α1	–	+	+	+	–	+
Norepinephrine (0.01–3 μg/kg/min)	Potent α1 agonist, modest β1,β2 agonist	–	+	+	+	–	+
Epinephrine (0.01–0.10 μg/kg/min)	Stimulates β1,β2, and α1 receptors	–	+	+	+	–	+

cGMP cyclic guanosine monophosphate, *NO* nitric oxide, *BNP* B-type natriuretic peptide

- Should be reserved for patients with hemodynamic instability or evidence of poor cardiac output and end organ hypoperfusion ("wet and cold"):
  - Systemic hypotension
  - Renal dysfunction

Milrinone

- Inhibits PDE-3, preventing degradation of cyclic adenosine monophosphate (cAMP)
  - Increased cAMP leads to vasodilation
- Reduces RV and LV pre-load and afterload
- Potent pulmonary vasodilator
- Can cause marked hypotension
- Does not act via adrenergic receptors thus may be more desirable in patients on chronic beta blocker therapy
- Increased incidence of atrial and ventricular arrhythmias [30]
- Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME-CHF) in which hospitalized patients were randomized to a 48-h infusion of intravenous milrinone or placebo demonstrated that administration of milrinone was associated with:
  - A higher rate of early treatment failure
  - More sustained hypotension
  - New atrial arrhythmias
  - Had a higher composite rate of death or rehospitalization
  - Patients with an ischemic etiology that were treated with milrinone had a higher 60-day mortality

Dobutamine

- Synthetic catecholamine
- Nonselective beta-1 and beta-2 adrenergic receptor agonist
- Positive inotropy and chronotropy
- Decreases afterload
- Increases heart rate, stroke volume and cardiac output
- Dose-related increase in risk for atrial and ventricular arrhythmia

Dopamine

- Dose-dependent activation of D1, beta-1, and alpha-1 receptors
- Low dose (2 mcg/kg/min)—activates vascular D1 receptors (coronary/renal/mesenteric)
- Moderate dose (2–5 mcg/kg/min)—binds to beta-1 receptors in the heart leading to inotropy
- High doses (5–15 mcg/kg/min)—activates alpha-1 receptors
- Dose-related increase in risk for atrial and ventricular arrhythmia

Mechanical Circulatory Support

In patients who have a persistent low output state ("cold") despite medical management, immediate consideration should be made for initiation of mechanical circulatory support

- Conditions in which MCS is generally accepted:
  - Fulminant myocarditis with cardiogenic shock
  - Acute hemodynamic compromise

    - Cardiopulmonary arrest
    - Cardiogenic shock
  - High risk percutaneous coronary interventions
  - In patients who are waiting for heart transplantation

The devices below specifically address acute needs and are for short term support only, and can be used for days to weeks. Long term devices can be used in patients waiting for transplant and are discussed in Chapter 25. A variety of devices are available, the ones most commonly used in clinical practice will be discussed here

Intraaortic Balloon Counterpulsation

- Most well studied
  - Data are mixed regarding effectiveness in those with cardiogenic shock after acute MI
- Increases coronary blood flow, decreases myocardial demand and increases oxygen supply, increases cardiac output
- Contraindications:
  - Aortic dissection
  - Severe aortic regurgitation (AR)
  - Severe peripheral arterial disease (PAD) (occlusive aortoiliac disease)

Percutaneous Ventricular Assist Devices (VAD)

- Impella
  - Uses a miniature impeller pump that is placed across the aortic valve into the LV; draws blood out of the ventricle and ejects blood through the ascending aorta
  - Can pump 2.5 or 5.0 L/min depending on size of pump used
  - Requires systemic anticoagulation
  - Can be used to vent the LV in patients on extracorporeal membrane oxygenation (ECMO) support
  - Contraindications—mechanical aortic valve, moderate-severe aortic valve disease, LV thrombus, moderate-severe peripheral arterial disease
- Tandem heart [31]
  - Left atrial-to-femoral artery bypass system using:
    - Transseptal cannula
    - Arterial cannula
    - Centrifugal blood pump
  - Provides flow rates up to 4.0 L/min
  - Requires systemic anticoagulation
  - Contraindications—ventricular septal defect, RV failure, left atrial thrombus, aortic insufficiency, aortic dissection, moderate-severe peripheral arterial disease
- ECMO [32]
  - Provides total circulatory support
  - Uses a centrifugal pump and membrane oxygenator
  - Can be placed percutaneously
  - Supports both the left and right ventricle
  - Requires systemic anticoagulation
  - Two types: venoarterial and venovenous
    - Only venoarterial ECMO provides hemodynamic support
    - Both venoarterial and venovenous provide respiratory support

– Contraindications—age >75 years, irreversible pulmonary or cardiac disease, metastatic malignancy, significant brain injury, end-stage renal/liver/lung disease, contraindication to anticoagulation

Complications of Mechanical Circulatory Support

- Infection
- Thrombosis
- Thrombocytopenia
- Hemolysis
- Bleeding
- CVA

MAINTENANCE THERAPY FOR HF

Once the acute episode has been initially managed, focus should shift toward education of the patient and initiation of medications that will promote neurohormonal blockade and prolonged survival (see Chap. 25)

Major society guidelines recommend the following agents for patients who have HF with reduced systolic function [12]:

A. Beta blocker therapy [33–35]

- Approved agents for HFrEF: bisoprolol, carvedilol, and metoprolol succinate (XL)
- For those taking beta blockers on admission, in absence of cardiogenic shock (i.e. the typical "wet/warm" presentation): continue without dose adjustment until decongested
- For those not taking beta blockers on admission: avoid initiation during acute congestion but then initiate low dose prior to discharge
- For both established or de novo HF: avoid use of beta blockers in those with shock (i.e. "cold") presentations
- Slowly uptitrate as an outpatient

B. ARNI [12]

- No data on inpatient initiation but should be considered in all patients with an LVEF <40% and NYHA II–III symptoms on an outpatient basis; should replace ACEi/ARB in outpatient setting

C. ACEi [36–38]

- Should be initiated prior to discharge in all patients with LV systolic dysfunction and slowly uptitrated
- Aggressive titration prior to stabilization of low output states can lead to decompensation
- Contraindications—pregnancy, previous angioedema, previous hypersensitivity, bilateral renal artery stenosis, hyperkalemia (K >5.5)

D. ARB [39]

- Administer to those patients intolerant to ACEi
- Similar contraindications to ACEi

E. Aldosterone antagonists [40]

- In patients already receiving ACEi/ARB/ARNI with symptomatic HF (NYHA class II–VI)
- Use with caution in those with significant renal dysfunction (serum creatinine ≤2.5 mg/dL in men and ≤2.0 mg/dL) or a history of hyperkalemia
- Initiation during acute decompensation of HF is relatively poorly studied

F. Hydralazine + Isosorbide dinitrate

- Certain populations [41]
  - Consider if intolerant to ACEi/ARB/ARNI
  - Significant increased survival in self-described African Americans in the Veterans Administration Cooperative Vasodilator—Heart Failure Trial (V-HeFT) trial
  - Initiation during acute decompensation of HF is relatively poorly studied, but probably safe

G. ICD [42, 43]

- Consider in patients with LVEF ≤35% (ischemic or non-ischemic) and persistent NYHA class II–III HF despite maximum tolerable medical therapy
- For de novo acute HF, ICD implantation should be deferred for up to 90 days to allow for initiation and titration of GDMT and promote recovery of LV function

H. CRT [44]

- Consider in patients with LVEF ≤35% (ischemic or non-ischemic) and persistent NYHA class III or ambulatory class IV HF despite maximum tolerable medical therapy and a QRS duration ≥120 ms
- For de novo acute HF, CRT should be deferred to allow for initiation and titration of GDMT and promote recovery of LV function

QUESTIONS

1. A 28-year-old previously healthy gentleman is brought to the emergency department by his wife after she noticed mild confusion, weakness, fatigue, and dyspnea. She also notes that he has had a persistent nocturnal cough for the past 7 days. Approximately 10 days prior, he developed fevers, chills and myalgias; this was accompanied by a nonproductive cough and mild dyspnea. His fevers and myalgias resolved spontaneously, but she has noted a progressive decline in his energy level since. They have a 4-year-old son, and he has had difficulty keeping up with him on the playground. He has no prior medical history, and does not take any medications or dietary supplements. On exam, he is obtunded. VS: Afebrile. BP 78/60 mmHg, HR 118. Pulse oximetry 93% on RA. Height: 69 inches, weight: 165 pounds. Extremities are cool. There is no lower extremity edema. Heart sounds are regular with an audible S1 and S2. There is an S3 gallop noted. There is a faint holosystolic murmur at the LV apex which does not radiate. His neck veins are distended to 15 cm of water. Laboratory studies reveal a normal CBC, normal TSH, BUN 35 mg/dL, Creatinine 1.95 mg/dL, AST 1235 U, ALT 1412 U, Lactic acid 7.6, TnI 0.53 ng/mL (normal <0.03), NT-proBNP 23,055 pg/mL. ECG: Sinus tachycardia. CXR shows a mildly enlarged cardiac silhouette and dilated upper lobe vessels.

   Initial management of the patient includes all the following EXCEPT:
   A. Oxygen therapy via nasal cannula
   B. IV enalaprilat
   C. IV dobutamine
   D. Consideration of placement of a PA line
   E. Loop diuretics

   Answer: B. The patient has clinical evidence of hemodynamic instability, including, hypotension, sinus tachycardia, change in mental status, lactic acidosis and evidence of end organ dysfunction. Initial management should be aimed at restoration of hemodynamics and relief of symptoms. Initiation of an ACEi during profound shock could lead to worsening hemodynamics, and preferred agents would be those named at improving inotropy.

2. Regarding the patient in question 1, you choose to empirically start dopamine, but despite escalating doses, the patient remains cool, systolic blood pressure remains below 80 mm Hg, and the patient becomes anuric. He developed acute respiratory distress with worsening confusion, and is intubated. A pulmonary artery catheter is emergently placed, and demonstrates the following hemodynamics: RA 18 mmHg, PA 35/20 mmHg MPAP 25 mmHg, PCWP 20 mmHg, mixed venous oxygen saturation 34%, cardiac output 2.1 L/min. A bedside echocardiogram is performed and shows severe biventricular function, with an LVEF of 8%.

   What would be the next best option for this patient to support his hemodynamics?
   A. IV Nitroglycerin
   B. Ultrafiltration
   C. Placement of an intra-aortic balloon pump
   D. Placement of ECMO
   E. Nesiritide

   Answer: D. This patient has profound cardiogenic shock. It is unlikely that pharmacologic agents will be enough to support his hemodynamics. An intra-aortic balloon pump would provide some support to the left heart, but he has severe right ventricular

failure as well, evidenced by his high right atrial pressure and high PCWP; they are essential equivalent. Vasodilators are contraindicated due to hypotension. ECMO provides total circulatory support and is the appropriate choice in patients who have evidence of severe right ventricular failure or who have significant hypoxia related to their LV failure. Ultrafiltration can be considered after the patient is placed on ECMO.

3. Is an endomyocardial biopsy reasonable in this setting?
   A. Yes
   B. No

   Answer: A. Endomyocardial biopsy is indicated in patients who present with acute onset of heart failure symptoms of less than 2 weeks' duration and hemodynamic compromise. It is an ACC/AHA class IB indication [12].

4. Which of the following is the most likely diagnosis in this patient:
   A. Acute myocardial infarction
   B. Pulmonary embolism
   C. Chronic active myocarditis
   D. Fulminant myocarditis
   E. Hypovolemic shock

   Answer: D. This patient has fulminant myocarditis, which is characterized by acute onset of illness and profound cardiogenic shock. If a patient with fulminant myocarditis is recognized early on and aggressive treatment is administered, more than 90% of patients will develop a full recovery [45], with minimal long-term sequela. Fulminant myocarditis, when recognized and treated early as an excellent prognosis. In contrast to patients with acute myocarditis, who usually present with a less profound symptoms, and may go on to develop chronic, stable congestive HF, and can sometimes progressed to end-stage cardiomyopathy requiring cardiac transplantation. The differential diagnosis of the patients who presents with new onset, acute HF with cardiogenic shock include acute myocardial infarction, necrotizing eosinophilic myocarditis, giant cell myocarditis, peripartum cardiomyopathy, and sarcoidosis. Patients with fulminant myocarditis typically present with a flulike prodrome 2–4 weeks prior and frequently present with NYHA class IV symptoms and physical exam findings consistent with cardiogenic shock and hemodynamic compromise. This contrasts with those who have acute, non-fulminant myocarditis, who typically present with milder symptoms. With aggressive management, most patients with fulminant myocarditis will experience complete recovery of their ventricular function within several weeks after onset of symptoms [46].

5. A 65-year-old woman with a 4-year history of dilated cardiomyopathy, LVEF of 20–25%, presents with a progressive weight gain of approximately 18 pounds, worsening dyspnea on exertion and progressive lower extremity edema. She now has dyspnea after walking several steps. She has no other medical history. She adheres to a sodium restricted diet and drinks no more than 2 L of fluids per day. She has not missed any medications, and records when medications are taken. She does her own cooking and avoids processed foods. Denies fevers or chills. Current medications are lisinopril 5 mg daily, carvedilol 12.5 mg PO BID, furosemide 80 mg PO BID and spironolactone 25 mg PO Daily. VS: Afebrile, BP 128/65 mmHg, HR 98, Pox 95% on RA. CXR demonstrates mild pulmonary edema. ECG shows atrial fibrillation with a ventricular rate of 92 beats per min, her QRS duration is 102 ms. She has no history of atrial fibrillation.

   What is the most likely cause of her acute decompensation?
   A. Atrioventricular dyssynchrony
   B. Intraventricular dyssynchrony
   C. Dietary indiscretion
   D. Pneumonia
   E. Medication noncompliance

   Answer: A. Patients with LV systolic dysfunction and chronic HF often do not tolerate the atrioventricular dyssynchrony that occurs when atrial fibrillation develops, and worsening of HF symptoms occur. Management should be aimed at decongestion followed by restoration of sinus rhythm.

6. Which of the following statements regarding IV milrinone is false:
   A. It is a more potent pulmonary vasodilator than dobutamine
   B. It has been shown to decrease morbidity and length of hospital stay
   C. It prevents the breakdown of cAMP
   D. It has arrhythmogenic potential
   E. It increases myocardial oxygen consumption

   Answer: B. The OPTIME-CHF trial showed that treatment with milrinone was associated with a (non-significant) higher number of deaths, and no difference in length of hospital stay compared to placebo.

7. A 59-year-old gentleman presents for evaluation of progressive dyspnea, orthopnea, and lower extremity edema. He has a history of hypertension and complete heart block and had a dual chamber pacemaker placed approximately 1 year ago. He denies anginal symptoms. Exam reveals an S3 gallop, III/VI holosystolic murmur at the apex, distended neck veins and 2+ bilateral lower extremity edema. His ECG demonstrates 100% VVI pacing at 60 beats per min. A stress test was previously ordered by his primary care physician which revealed no evidence for ischemia, however, his LVEF was 28%. Current medications are aspirin and lisinopril.

   After he is treated with furosemide and decongested, which of the following medications should be started next?
   A. Digoxin
   B. Verapamil
   C. Bisoprolol
   D. Isosorbide mononitrate
   E. Hydralazine

   Answer: C. Initiation of beta blocker therapy in patients with HFrEF is a class IA recommendation per the ACC/AHA guidelines, and should be initiated once the patient is no longer acutely decompensated. Bisoprolol has been studied in the HFrEF population. Digoxin [47] does not confer a survival advantage and should be reserved for patients who are on optimal HF therapy and who have persistent NHYA class III, or in patients with atrial fibrillation in need of more optimal rate control. Verapamil should not be used in patients with HFrEF; its negative inotropic effects could lead to acute decompensation. Isosorbide mononitrate and hydralazine have been shown to be effective in certain populations (i.e. African Americans), but these agents would not be the appropriate choice as first line therapy.

8. A 56-year-old woman with a history of hypertension and PAD is brought to the emergency department by paramedics after awakening with acute dyspnea. Upon arrival, she is tachypneic and

hypoxic, and is emergently intubated. VS upon arrival: BP 230/118 mmHg, HR 97, Pox 84% on 2 L nasal cannula, respiratory rate 28. Exam reveals elevated JVP, regular rhythm and an S4 gallop. Lungs have diffuse crackles. Before intubation, she reported no dietary indiscretions. A 2-D echocardiogram done 6 months prior showed normal LV function with LV hypertrophy, normal RV function and no valvular abnormalities. Labs: Na 135 mmol, K 4.1 mg/dL, BUN 35 mg/dL, Cr 2.75 mg/dL. CBC, troponin and LFT's are normal. CXR shows diffuse alveolar infiltrated and peribronchial cuffing. ECG shows normal sinus rhythm with LV hypertrophy and no ischemic changes or evidence of prior infarction.

As part of her evaluation, which of the following tests should be ordered to identify the etiology of her decompensation?

A. Coronary angiogram
B. Renal duplex Doppler ultrasound
C. V/Q Scan
D. Cardiac MRI
E. Bronchoscopy

Answer: B. This patient has renal artery stenosis and renovascular hypertension. She likely has diastolic dysfunction in the setting of longstanding hypertension. She developed flash pulmonary edema which is more common in patients with bilateral renal artery stenosis than unilateral stenosis [48].

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CHAPTER 25

DANIEL A. ZLOTOFF AND JENNIFER E. HO

Chronic and End-Stage Heart Failure

CHAPTER OUTLINE

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
AHA	American Heart Association
ARB	Angiotensin-receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
BB	Beta-blocker
BMI	Body mass index
BNP	B-type natriuretic peptide
BTT	Bridge to transplantation
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
CO	Cardiac output
CPET	Cardiopulmonary exercise test
Cr	Creatinine
CV	Cardiovascular
DT	Destination therapy
HCM	Hypertrophic cardiomyopathy
HDZ	Hydralazine
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HTN	Hypertension
IABP	Intra-aortic balloon pump
ICD	Implantable cardiac defibrillator
ISDN	Isosorbide dinitrate
JVP	Jugular venous pressure
K	Potassium
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MCS	Mechanical circulatory support

MI	Myocardial infarction
NIDCM	Nonischemic dilated cardiomyopathy
NYHA	New York Heart Association
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
RRR	Relative risk reduction
RV	Right ventricular
RVEF	Right ventricular ejection fraction
SCD	Sudden cardiac death
TPG	Transpulmonary gradient
TTE	Transthoracic echocardiogram
VO_2	Peak oxygen consumption
WU	Woods Units

DEFINITION OF HF

a) Inability of the heart to pump enough blood to meet metabolic needs of tissues, or to do so at the expense of elevated filling pressures
b) Can be caused by inability of ventricle to fill, inability to pump, or systemic process causing excess metabolic demand
c) American Heart Association (AHA) Classification—based on disease progression and therapeutic strategy
    i) Stage A—high risk for development of HF without evidence of structural heart disease or symptoms of HF
    ii) Stage B—structural heart disease but without symptoms or signs of HF
    iii) Stage C—structural heart disease and current or prior symptoms of HF
    iv) Stage D—refractory HF requiring advanced therapies
d) New York Heart Association (NYHA) classification—based on symptoms
    i) Class I—no limitation of ordinary physical activity
    ii) Class II—mild symptoms with ordinary physical activity
    iii) Class III—marked limitation of physical activity; often subdivided into class IIIa (without dyspnea at rest) and class IIIb (with recent dyspnea at rest)
    iv) Class IV—symptoms of HF at rest or with minimal physical activity

CAUSES OF CHRONIC HF

a) Ischemic cardiomyopathy—coronary artery disease (CAD) most common cause of left ventricular (LV) systolic dysfunction in developed countries
    i) MI → regional scar and loss of contractility → adverse remodeling of remaining segments → LV dilatation and dysfunction
b) Nonischemic cardiomyopathy (NICM)
    i) Idiopathic—up to 50%
    ii) Toxins—potentially reversible with removal of offending agent
        (1) Alcohol
        (2) Cocaine—pathophysiology may include coronary vasospasm, direct myocardial toxicity
        (3) Medications (anthracyclines, trastuzumab, cyclophosphamide)
    iii) Hypertension (HTN)

(1) Initially causes concentric LV hypertrophy (LVH) but can eventually progress to dilated cardiomyopathy

iv) Viral myocarditis

(1) Initial infection may present acutely or may be silent

v) Other infectious causes

(1) HIV—associated with high viral titers
(2) Chagas Disease—prevalent in Central and South America
(3) Lyme Disease—typically associated with conduction disturbances

vi) Genetic

(1) Familial dilated cardiomyopathy
(2) LV non-compaction
(3) Arrhythmogenic right ventricular cardiomyopathy

vii) Tachycardia-induced cardiomyopathy

(1) Can be due to atrial arrhythmias, ventricular arrhythmias, or premature ventricular contractions
(2) Resolves with control of heart rate or elimination of arrhythmia

viii) Peripartum Cardiomyopathy

(1) Occurs in last month of pregnancy or within 5 months of delivery
(2) LV function usually improves but high rate of recurrent dysfunction with subsequent pregnancies

ix) Endocrine

(1) Hypothyroidism
(2) Pheochromocytoma
(3) Acromegaly
(4) Thiamine deficiency

c) HF with preserved Ejection Fraction (HFpEF)

i) LV ejection fraction (LVEF) ≥50% in approximately half of all HF patients [1]
ii) Compared to patients with heart failure with reduced ejection fraction (HFrEF), HFpEF patients are more likely to be older, female, hypertensive, and have atrial fibrillation (AF) [2]
iii) No treatments proven to prolong survival or decrease HF hospitalizations in HFpEF patients

d) Valvular heart disease

i) Any valvular lesion can cause HF symptoms in presence or absence of LV systolic dysfunction; **please see chapters 20 and 21 for additional details**

e) Hypertrophic cardiomyopathy (HCM): **please see chapter 26**
f) Restrictive cardiomyopathy: **please see chapter 26**
g) Right ventricular (RV) failure

i) Almost always associated with pulmonary hypertension (PH)
ii) Final consequence of many congenital heart lesions, particularly in context of Eisenmenger syndrome (irreversible PH)

h) Constrictive Pericarditis: **please see chapter 10**

PATHOPHYSIOLOGY OF CHRONIC HF

a) Acute injury to myocardium causes decreased cardiac output (CO) and end-organ perfusion
b) Neurohormonal activation (see Fig. 25-1)
    i) Upregulation of renin-angiotensin-aldosterone system
        (1) Increased angiotensin II → systemic and renal arterial vasoconstriction
        (2) Increased aldosterone → renal sodium retention
    ii) Sympathetic nervous system activation
        (1) Release of catecholamines (e.g. norepinephrine)
        (2) Results in enhanced myocardial contractility and systemic vasoconstriction
        (3) Decreased distal water delivery to kidney → decreased excretion of water
    iii) Release of anti-diuretic hormone

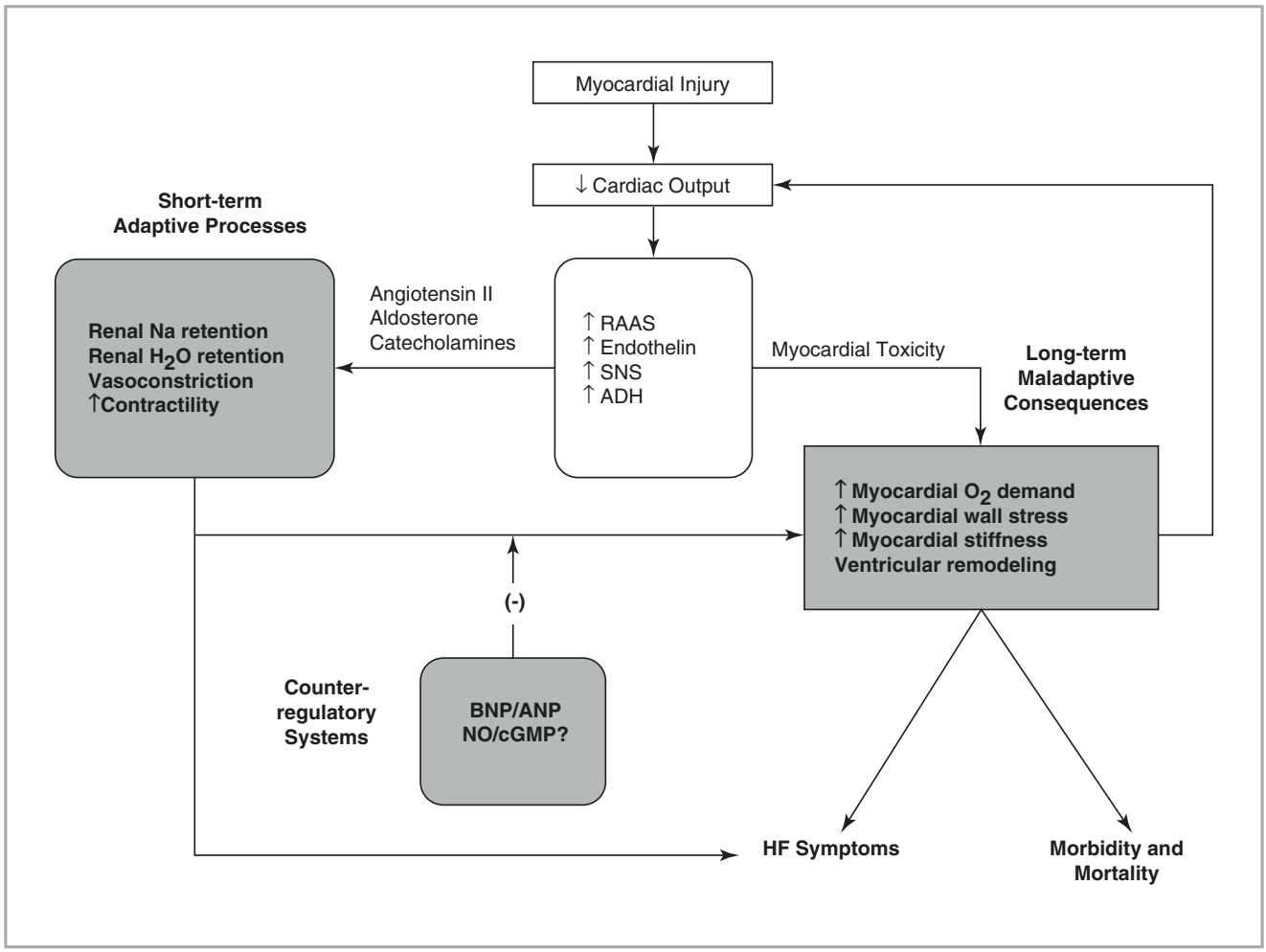


FIGURE 25-1

A schematic representation of the pathophysiology of chronic heart failure due to impaired LV systolic function. The initiating event is an injury that leads to myocardial dysfunction. The body compensates for decreased cardiac output by activating multiple neurohormonal systems. In the acute phase, these mechanisms act to maintain perfusion of systemic organs, but may also result in congestion and HF symptoms. Over time, these compensatory systems have adverse effects on the LV, stimulating further neurohormonal activation, worsening HF symptoms, and ultimately leading to HF mortality. Counter-regulatory systems, including the natriuretic peptides, are upregulated to prevent the adverse effects of neurohormonal activation. *RAAS* renin-angiotensin-aldosterone system, *SNS* sympathetic nervous system, *ADH* anti-diuretic hormone, *BNP* B-type natriuretic peptide, *ANP* atrial natriuretic peptide, *NO* nitric oxide, *cGMP* cyclic guanosine monophosphate, *HF* heart failure

(1) Enhances reabsorption of water by renal collecting tubules

iv) Ventricular remodeling

(1) Type of remodeling depends on type of stress placed on ventricle
(2) Pressure overload (e.g. aortic stenosis)

(a) Concentric remodeling → LVH → reduced wall stress per LaPlace's Law

(3) Volume overload

(a) Eccentric remodeling → ventricular dilatation
(b) Increased preload maintains cardiac output via Frank-Starling mechanism

(4) Myocardial injury (e.g. MI)

(a) Stretching of scarred tissue → mixed pressure and volume load on non-infarcted tissue
(b) Ventricular dilatation → maintenance of cardiac output

(5) Acute compensatory responses become deleterious over time

(a) Progressive ventricular dilatation → increased wall stress per LaPlace's Law
(b) Ongoing ventricular remodeling causes progressive HF

EVALUATION OF CHRONIC HF

Please see chapters 26 (Cardiomyopathies) and 24 (Acute Heart Failure) for additional details regarding the initial evaluation of heart failure

a) Evaluation of acute versus chronic HF

i) Symptoms of acute heart failure and chronic heart failure are similar, reflecting congestion and low cardiac output (CO)
ii) Features more specific to chronic HF than acute HF include:

(1) Unintended weight loss [3]
(2) Volume overload refractory to diuretics

b) Diagnostic evaluation of chronic HF: directed at determining prognosis

i) Transthoracic echocardiogram: often shows dilated chambers, and LV dilation is a poor prognostic factor
ii) Cardiopulmonary exercise testing (CPET): measures peak oxygen uptake (VO_2), provides relative contributions of cardiac and pulmonary disease to dyspnea, and offers prognostic information
iii) Right heart catheterization: required when considering advanced therapies

PROGNOSIS OF CHRONIC HF

a) Factors associated with worse prognosis in chronic HF include:

i) LVEF—39% increase in mortality for each 10% drop in LVEF [4]
ii) RV ejection fraction (RVEF) <35% [5]
iii) PH [6]
iv) QRS length >120 ms [7]
v) Peak VO_2 < 14 mL/kg/min [8]
vi) Chronic kidney disease—patients with severe renal dysfunction have 2× risk of death at 1 year compared to patients with normal renal function [9]
vii) B-type Natriuretic Peptide (BNP)/N-terminal (NT)-proBNP—one of strongest independent predictors of prognosis [10]
viii) Troponin levels [11]

b) HFpEF has similar prognosis to HFrEF—median survival of 2.1 years from diagnosis [2]
c) Risk scores have been developed for patient risk stratification
    i) Seattle Heart Failure Model
        (1) Incorporates clinical variables, medications, and devices
        (2) Highly accurate prediction of survival out to 3 years in general HF population [12]
    ii) Heart Failure Survival Score
        (1) Incorporates CAD, heart rate, LVEF, blood pressure, intraventricular conduction delay, serum sodium, peak VO_2
        (2) Used to risk-stratify patients being considered for transplantation

MANAGEMENT OF CHRONIC HF

a) Treatment of comorbid conditions
    i) Hypertension
    ii) Hyperlipidemia
    iii) Diabetes
    iv) Atrial fibrillation
        (1) Control of ventricular rate
        (2) Rhythm control
            (a) No survival benefit has been demonstrated but may improve symptoms
            (b) Amiodarone and dofetilide are the only antiarrhythmic agents with established safety in HF
            (c) Anticoagulation according to CHA_2DS_2-VASc risk score
    v) CAD
        (1) Treatment of angina with nitrates and beta-blockers
        (2) Consideration of revascularization when indicated
            (a) CABG provides superior long-term survival compared to medical management for patients with EF <35% and CAD suitable for revascularization [13]
    vi) Ventricular arrhythmias
        (a) Antiarrhythmics for symptomatic ventricular arrhythmias only
        (b) No survival benefit to antiarrhythmic treatment of asymptomatic ventricular arrhythmias
    vii) Thyroid disorders
b) Ongoing routine clinical assessment
    i) Functional status
    ii) Volume status
    iii) Weight
    iv) Dietary compliance
    v) Minimize use of cardiotoxins
c) Chronic surveillance
    i) Repeat TTE as needed to determine response to therapy
    ii) A role for BNP/NT-proBNP-guided medical therapy remains unclear

d) Dietary modification

   i) Sodium and fluid restriction for patients with signs or symptoms of congestion

e) Medical therapy (see Tables 25-1 and 25-2).

   i) Primary goal of HFrEF therapy is to interrupt neurohormonal activation → prevent LV remodeling → improve symptoms and reduce mortality. Guideline-directed medical therapy is summarized in Table 25-1. Newer agents including sodium-glucose co-transporter 2 (SGLT2) inhibitors and soluble guanylate cyclase (sGC) stim-

TABLE 25-1

MEDICAL THERAPIES FOR PATIENTS WITH LV SYSTOLIC DYSFUNCTION (ACC/AHA STAGE B–D)

THERAPY	MORTALITY OR MORBIDITY BENEFIT	RECOMMENDATION	COMMENTS
ACE-inhibitors	■ Stage B: 20% RRR death or hospitalization [16] ■ Stage C: 16% RRR death at 4 years [17] ■ NYHA Class IV: 31% RRR death at 1 year [18]	■ Class I recommendation	■ Should be used in all patients with LVEF <40% unless intolerant ■ Need to monitor Cr, K on therapy
Angiotensin-receptor blockers	■ Stage C: 23% RRR of death or HF hospitalization at 3 years in ACEI intolerant patients [19] ■ Combination ACEI/ARB: no ↓ mortality but ↓ in HF hospitalizations [20]	■ Class I recommendation for patients intolerant of ACEI	■ No data for Stage B but reasonable to use if ACEI-intolerant ■ Combination ACEI/ARB has more complications (↑Cr, ↑K)
Beta-blockers	■ Stage B: 30% RRR CV death, 21% RRR for symptomatic HF [21] ■ Stage C: 34% RRR mortality, 41–44% RRR SCD at 1 year [22] ■ NYHA Class IV: 35% RRR mortality at 10 months [23]	■ Class I recommendation	■ Only metoprolol succinate, carvedilol, and bisoprolol have proven mortality benefit ■ Should be used in all Stage B and Stage C patients ■ Use with caution in patients with low CO
Angiotensin receptor-neprilysin inhibitor	■ NYHA Class II–IV: 20% RRR CV death or HF hospitalization compared to ACEI [24] ■ NYHA Class II–IV: 26% RRR in all-cause readmission and 38% RRR in HF readmission compared to ACEI [25]	■ Class I recommendation for NYHA class II–III patients	■ Sacubitril-valsartan is only member of class currently approved in the US ■ Patients tolerant of ACEI or ARB should be switched to ARNI ■ Do not administer within 36 h of last dose of ACEI ■ Contraindicated in patients with history of angioedema
Aldosterone antagonists	■ NYHA Class III–IV: 30% RRR mortality at 2 years [26] ■ NYHA Class II: 37% RRR CV death or HF hospitalization [27] ■ Post MI LVEF <40%: 15% RRR mortality, 21% RRR SCD at 16 months [28]	■ Class I recommendation for NYHA II-IV and EF <35% ■ Class I recommendation for patients post-MI with EF <40% and either symptomatic HF or DM	■ Only studied in LVEF <35–40% ■ Should not be used if Cr >2.5 mg/dL in men or >2.0 mg/dL in women or K >5.0 meq/L ■ Avoid with ACEI + ARB combination (↑Cr, ↑K)

TABLE 25-1

(CONTINUED)

THERAPY	MORTALITY OR MORBIDITY BENEFIT	RECOMMENDATION	COMMENTS
Diuretics	■ Provide relief of symptoms related to congestion ■ No known mortality benefit	■ Class I recommendation in patients with fluid retention	■ May precipitate ↓K → arrhythmias
Hydralazine/ nitrates combination	■ 34% RRR mortality compared to placebo at 2 years but inferior to ACEI [29] ■ African-Americans: 43% RRR mortality and 33% RRR HF hospitalization with addition of HDZ/ISDN to ACEI and BB [30]	■ Class I recommendation for self-described African-Americans with NYHA class III-IV HF already on ACEI and BB ■ Class IIa recommendation for patients who cannot take ACEI or ARB	■ Can be used in substitution of ACEI/ ARB in intolerant patients ■ Addition to optimal therapy recommended in African-Americans
Ivabradine	■ NYHA Class II-IV with EF ≤35%: 18% RRR for CV death or HF hospitalization [31]	■ Class IIa recommendation for NYHA class II-III patients with LVEF ≤35% on BB at maximum tolerated dose in sinus rhythm with a heart rate of 70 bpm or greater at rest	■ Functions by selectively inhibiting the *If* current in the sinoatrial node to reduce heart rate
Digoxin	■ No effect on mortality; 28% RRR HF hospitalizations at 3 years [32]	■ Class IIa recommendation	■ Should not be used in Stage B patients unless for AF rate control

ACE Angiotensin-Converting Enzyme, *RRR* Relative Risk Reduction, *NYHA* New York Heart Association, *LVEF* Left Ventricular Ejection Fraction, *Cr* Creatinine, *K* Potassium, *HF* Heart Failure, *ACEI* Angiotensin-Converting Enzyme Inhibitor, *ARB* Angiotensin-Receptor Blocker, *CV* Cardiovascular, *SCD* Sudden Cardiac Death, *CO* Cardiac Output, *ARNI* Angiotensin Receptor-Neprilysin Inhibitor, *MI* Myocardial Infarction, *DM* Diabetes Mellitus, *BB* Beta-Blocker, *HDZ* Hydralazine, *ISDN* Isosorbide Dinitrate, *AF* Atrial Fibrillation

TABLE 25-2

MEDICAL THERAPIES HARMFUL TO PATIENTS WITH LV SYSTOLIC DYSFUNCTION (ACC/AHA STAGE B–D) [33]

THERAPY	COMMENTS
Calcium channel blockers	■ First generation dihydropyridines or non-dihydropyridines may have negative inotropic effect ■ Amlodipine and felodipine are considered safe in HFrEF
NSAIDs	■ Can cause volume overload through increased renal sodium and fluid retention
Diabetes medications	■ Thiazolidinediones can cause volume overload through increased renal sodium retention ■ DPP-4 inhibitors (e.g. sitagliptin, saxagliptin) demonstrated to increase HF hospitalizations
Inotropes	■ Increase the risk of ventricular arrhythmias ■ Used in the outpatient setting only for symptom palliation
Antiarrhythmics	■ Class I agents flecainide and disopyramide and certain class III agents including dronedarone and sotalol have negative inotropic and pro-arrhythmic properties

HFrEF Heart Failure With Reduced Ejection Fraction, *NSAID* Nonsteroidal Anti-Inflammatory Drug, *DPP-4* Dipeptidyl Peptidase-4, *HF* Heart Failure

ulators have been recently shown to improve outcomes in HFrEF patients when used in addition to existing guideline directed medical therapy [14, 15]

f) Device Therapy

i) Implantable cardiac defibrillators (ICDs) reduce incidence of sudden cardiac death in symptomatic patients with an LVEF <35% (**see Chapter 17 Ventricular Arrhythmias and Defibrillators**)
ii) Cardiac resynchronization therapy can improve symptoms and reduce mortality in NYHA Class II–IV patients with LVEF <35% and QRS >120 ms (**see Chapter 16 Bradycardia and Pacemakers/CRT**)
iii) Implantation of a pulmonary artery pressure monitor (CardioMEMS™) decreases hospitalizations and is approved for NYHA class III HF (HFrEF or HFpEF) patients who are on optimal medical therapy, and had a HF hospitalization in the previous year [34]

g) Exercise Training

i) Significant improvements in exercise capacity and peak VO_2 in HFrEF patients but no effect on mortality or hospitalizations [35]

h) HFpEF

i) No therapy has been shown to reduce mortality in HFpEF patients
ii) Focus of medical therapy is symptom reduction

(1) Diuretics (class I recommendation)
(2) Management of hypertension (class I recommendation)
(3) Control of ventricular rate in atrial arrhythmias
(4) Revascularization if symptomatic ischemia

iii) Cardioversion of AF to sinus rhythm may benefit selected HFpEF patients

ADVANCED HF

a) Characteristics of advanced HF (Table 25-3)

i) NYHA Class III–IV symptoms
ii) Difficulty with activities of daily living
iii) Frequent hospitalizations for HF
iv) Poor or inconsistent response to oral therapies
v) Inability to tolerate high doses of neurohormonal blockade due to hypotension or labile renal function
vi) Cardiac cachexia

b) Management of advanced HF (Fig. 25-2)

i) Patients should be referred to advanced HF center
ii) Strict fluid management to avoid HF exacerbations
iii) Often require escalating dose of loop diuretics or addition of thiazide diuretic to achieve effective diuresis
iv) Continue neurohormonal antagonists if tolerated with close attention to blood pressure, signs of low CO and/or renal function
v) Hospital admission for refractory volume overload or evidence of reduced peripheral perfusion
vi) Pulmonary artery catheterization may be useful

c) Inotropes

i) Work by increasing cyclic adenosine monophosphate (cAMP) → increased intracellular calcium stores → augmented contractility. Most commonly used agents are dobutamine, milrinone, and dopamine. **See detailed discussion in chapter 24 Acute Heart Failure**.

TABLE 25-3

FEATURES OF PATIENTS REQUIRING REFERRAL FOR ADVANCED THERAPIES [43]

■ Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA class III or IV) despite optimal medical and device therapy
■ Episodes of congestion and/or reduced cardiac output at rest
■ Refractory severe angina despite maximally-tolerated anti-anginal therapies and revascularization attempts
■ Intolerance of guideline-directed medical therapies due to hypotension
■ Volume overload refractory to diuretics
■ Refractory life-threatening ventricular arrhythmias or frequent ICD discharges
■ Objective evidence of severe cardiac dysfunction shown by at least 1 of the following:
a. LVEF < 30%
b. Pseudonormal or restrictive mitral inflow pattern
c. Mean PCWP >16 mm Hg and/or RAP >12 mm Hg by PA catheterization
d. High BNP or NT-proBNP plasma levels
■ Severe impairment of functional capacity shown by 1 of the following:
a. Inability to exercise
b. 6-min walk distance <300 m
c. Peak VO_2 < 14 mL/kg/min in absence of beta blocker or <12 mL/kg/min in presence of beta blocker
■ History of ≥1 HF hospitalization in past 6 months
■ Requirement for intravenous inotropic support
■ Presence of these features despite efforts to optimize all medical and device therapies

HF Heart Failure, *NYHA* New York Heart Association, *ICD* Implantable Cardioverter Defibrillator, *LVEF* Left Ventricular Ejection Fraction, *PCWP* Pulmonary Capillary Wedge Pressure, *RAP* Right Atrial Pressure, *PA* Pulmonary Artery, *BNP* B-Type Natriuretic Peptide

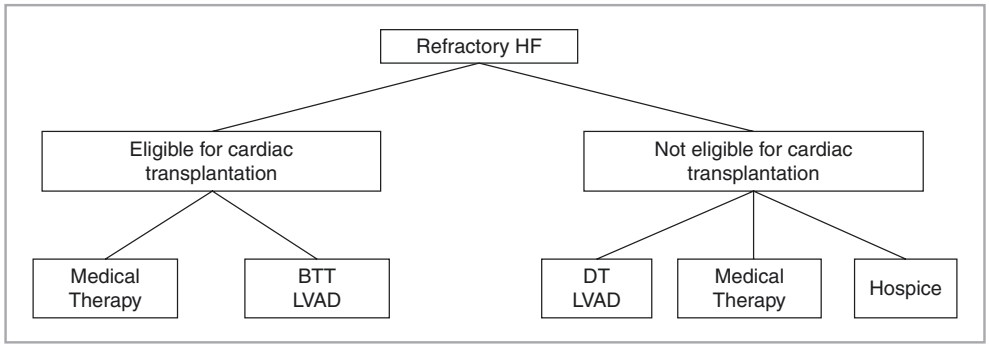


FIGURE 25-2

A general management approach to advanced HF. Each patient should be assessed for transplant eligibility. If listed for cardiac transplantation, decisions regarding the need for left ventricular assist device (LVAD) as a bridge-to-transplantation (BTT) should be individualized. For patients ineligible for transplantation, options include ongoing medical therapy, referral for LVAD as destination therapy (DT), or referral to hospice

ii) Consider in patients with reduced cardiac output and evidence of poor perfusion for short-term inpatient use or chronic outpatient use (palliative)
iii) Negative effects include:

(1) Arrhythmias (atrial and ventricular)
(2) Increased myocardial oxygen demand → ischemia
(3) Increased morbidity and mortality in clinical trials of inpatient and outpatient use [36]

iv) Chronic inotropic infusions should only be considered to reduce symptoms in patients waiting for cardiac transplantation or as a palliative measure in patients ineligible for transplant
v) Intermittent outpatient infusions of inotropes have not shown benefit in advanced HF

d) Palliative Care

i) Discussion of prognosis with patient and family is integral
ii) End-of-life care, including advanced directives, deactivation of ICD, and hospice care should be discussed with patients who have exhausted therapeutic options
iii) Inotropes, diuretics, and opiates are reasonable palliative medications

e) Left Ventricular Assist Devices (LVADs)

i) Pulsatile (first generation), axial/continuous-flow (second generation), and centrifugal/continuous flow (third generation) types
ii) Most contemporary devices are centrifugal/continuous-flow devices designed to unload LV and augment CO
iii) Inflow cannula placed in apex of LV and outflow cannula placed in ascending aorta
iv) Powered by external batteries through percutaneous drive line
v) Indications

(1) Bridge to Transplant (BTT)—option for patients on waiting list for cardiac transplantation who have long expected wait time

(a) Survival at 1 year 85–90% [37]
(b) May be able to reverse adverse consequences of advanced HF and improve overall condition prior to transplant

(i) Renal dysfunction from cardiorenal syndrome
(ii) Elevated pulmonary vascular resistance (PVR)
(iii) Liver injury from congestive hepatopathy
(iv) Cognitive impairment
(v) Cardiac cachexia

(c) Improved quality of life—80% achieve NYHA Class I or II by 3 months [38]

(2) Destination Therapy (DT)—patients with refractory HF who are not transplant candidates

(a) Survival significantly improved with first generation LVAD (HeartMate XVE) compared to inotropes (52 vs. 25% at 1 year) [39]
(b) Survival with second generation LVAD (HeartMate II) better than HeartMate XVE (68 vs. 55% at 1 years) [40]
(c) One year survival has improved to 74% for HeartMate II with clinical experience following FDA approval [41]
(d) One year survival of 88% with newest generation centrifugal-flow device (HeartMate 3) (data inclusive of patients implanted for both BTT and DT indications) [42] (Fig. 25-3)

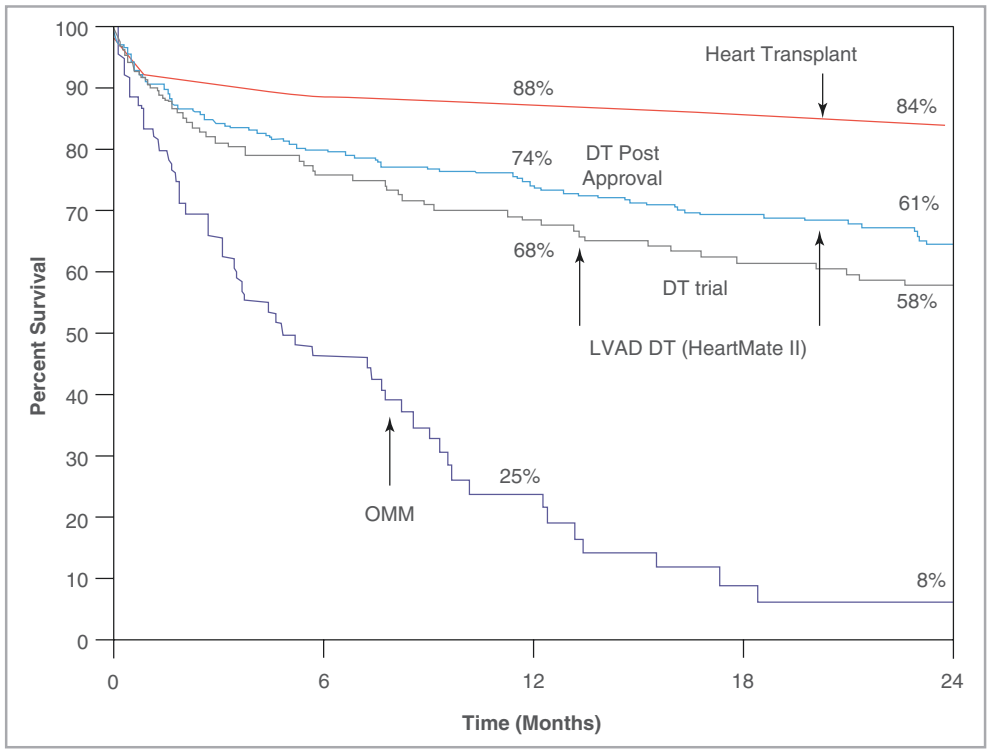
vi) Patient Selection

(1) Markers of high risk include:

(a) RV failure
(b) Hematological abnormalities
(c) Renal dysfunction

FIGURE 25-3

Survival curves for heart transplantation, LVAD (HeartMate II in both the DT trial and in real-world experience post-approval), and optimal medical management in the modern era. Reprinted with permission from Mancini et al. [45]



(d) Hepatic dysfunction
(e) Poor nutritional status

vii) Contraindications

(1) Irreversible end-organ failure
(2) Active infection
(3) Neurological injury with unclear recovery
(4) Inability to anticoagulate

viii) Complications of LVAD therapy

(1) Early postoperative

(a) Bleeding
(b) RV failure—may require placement of RV assist device

(2) Intermediate-term

(a) Infection—can occur in drive line that connects to power source (treated with antibiotics) or in device itself (which requires device exchange)
(b) Thromboembolism—all patients take anticoagulation unless intolerant
(c) Bleeding—patients develop acquired von Willebrand's disease → risk for intestinal bleeding from arteriovenous malformations

(3) Long-term

(a) Device failure—rare with second/third generation LVADs

f) Cardiac Transplantation (Tables 25-4 and 25-5)

i) Transplantation offers best long-term survival for patients with advanced HF—median survival of 10 years (Fig. 25-3) [44]
ii) Limited availability—approximately 2200 transplants/year in United States
iii) Evaluation for listing includes:

TABLE 25-4

INDICATIONS AND ABSOLUTE CONTRAINDICATIONS FOR CARDIAC TRANSPLANTATION

INDICATIONS	CONTRAINDICATIONS
Inotrope-dependence	Irreversible dysfunction of extracardiac organ
Advanced NYHA symptoms with poor short-term prognosis	Severe peripheral vascular disease
Refractory angina due to CAD without possibility of revascularization	Severe symptomatic cerebrovascular disease without possibility of revascularization
Refractory ventricular arrhythmias	Active infection
Unresectable low-grade myocardial tumors without metastases	Inadequate social support or inability to obtain medications
	Noncompliance

NYHA New York Heart Association, *CAD* Coronary Artery Disease

TABLE 25-5

RELATIVE CONTRAINDICATIONS FOR CARDIAC TRANSPLANTATION

RELATIVE CONTRAINDICATION	COMMENT
Age	Cutoff for age is center-dependent, but often <70. Limited data on outcomes in older age group
Malignancy	Can be listed after malignancy successfully treated; length of time post-treatment depends on malignancy
Obesity	BMI >30 kg/m^2 associated with worse outcomes
Fixed PH (PVR > 3 WU or TPG > 15 mmHg)	Can be listed if TPG or PVR can be lowered with medical therapy or mechanical therapy (IABP, LVAD)
Diabetes	Can be transplanted in absence of end-organ complications if diabetes can be controlled with diet and medication
Smoking and substance use disorder	Most centers require >6 months abstinence prior to listing
Recent pulmonary embolism	Requires anticoagulant therapy for 6–8 weeks
Poor social support or cognitive-behavioral disability	Must be able to demonstrate understanding and adherence to treatment plan, including immunosuppression and frequent follow up visits

BMI Body Mass Index, *PH* Pulmonary Hypertension, *PVR* Pulmonary Vascular Resistance, *WU* Woods Units, *TPG* Transpulmonary Gradient, *IABP* Intra-Aortic Balloon Pump, *LVAD* Left Ventricular Assist Device

(1) Right heart catheterization (RHC)

(a) Assessment of filling pressures and CO
(b) Determine need for inotropic therapy or mechanical circulatory support (MCS)
(c) Assess PH

(i) Increased risk of death if PA systolic pressure > 60 and PVR > 5 Woods Units (WU) or transpulmonary gradient (TPG) > 15 [46]
(ii) If transpulmonary gradient (TPG) > 15 or PVR > 3 WU, evaluate response to systemic or selective pulmonary vasodilator
(iii) Patients with reversibility of PH may benefit from inpatient tailored therapy to lower filling pressures or from MCS (intra-aortic balloon pump or LVAD) to unload LV
(iv) Sildenafil shown to improve exercise capacity and quality of life in patients with systolic HF with secondary PH; pulmonary vasodilators can worsen left-sided congestion and should be used cautiously [47]
(v) RHC can assess for changes in hemodynamics and urgency of transplantation

(2) CPET—can be used to assess functional status, prognosis and guide listing for transplant but should not be sole criteria used to assess patient eligibility

(a) Reasonable to consider transplant if:

(i) Peak VO_2 < 14 mL/kg/min in absence of beta-blocker
(ii) Peak VO_2 < 12 mL/kg/min in presence of beta-blocker
(iii) Peak VO_2 < 50% predicted peak VO_2

iv) Complications of cardiac transplantation

(1) Acute cellular rejection—T-cell mediated

(a) Managed with enhanced immunosuppression

(2) Humoral rejection—Antibody-mediated graft dysfunction

(a) Managed with enhanced immunosuppression
(b) May require antibody-depleting therapies

(3) Coronary allograft vasculopathy

(a) Progressive concentric intimal thickening of coronary arteries
(b) Leads to chronic graft dysfunction and sudden cardiac death
(c) May require repeat cardiac transplantation

(4) Infections

(a) Susceptible to opportunistic infections
(b) Increased rate of viral infections (e.g. cytomegalovirus)

(5) Malignancy

(a) Post-transplant lymphoproliferative disorder

(i) B-cell lymphoma induced by infection with Epstein-Barr Virus
(ii) Treated with reduction of immunosuppression, rituximab (anti-CD20 monoclonal antibody), and/or chemotherapy

(6) Drug Toxicities

(a) Calcineurin Inhibitors (tacrolimus, cyclosporine)—renal dysfunction, tremor, hyperkalemia
(b) Antimetabolites (mycophenolate mofetil, azathioprine)—bone marrow suppression
(c) Corticosteroids—hyperglycemia, osteoporosis, HTN, weight gain

REVIEW QUESTIONS

1. A 65 year old woman with a history of a myocardial infarction and LV systolic dysfunction with an LVEF of 28% comes to clinic for follow-up. She has a mild limitation of her exercise capacity due to dyspnea. She has been treated for HF for the past 6 months and is currently taking lisinopril 20 mg daily, carvedilol 6.25 mg twice a day, furosemide 40 mg daily, warfarin and potassium chloride. She continues to have dyspnea with moderate exertion. She reports compliance with her medications and adherence to a low sodium diet. An ICD was placed 3 months ago, and she has not had any shocks. Her blood pressure is 115/70 mmHg and heart rate is 90 bpm. The examination is notable for an irregular rhythm, a mitral regurgitation murmur and bibasilar crackles. Jugular venous pressure is mildly elevated and there is trace pitting edema in her lower extremities. The electrocardiogram shows atrial fibrillation with a QRS width of 110 ms. The serum sodium is 132 mmol/L, potassium 4.3 meq/L, BUN 45 mg/dL and creatinine 2.1 mg/dL. Liver function tests are normal. What is the best change to her current therapy to improve her long-term survival?
(a) Add losartan 25 mg daily
(b) Add spironolactone 25 mg daily
(c) Increase carvedilol to 12.5 mg twice a day

(d) Implant a cardiac resynchronization device
(e) Add digoxin 125 mg daily

2. Which of the following statements is true with regard to her atrial fibrillation?
   (a) Addition of digoxin would be useful to better control her ventricular response
   (b) Either amiodarone or sotalol would be a good choice for a rhythm control strategy
   (c) Sinus rhythm is preferable in patients with atrial fibrillation because it reduces mortality
   (d) Diltiazem is the best choice for an additional rate-control agent

3. An 81 year old woman with a history of hypertension is seen due to shortness of breath while climbing stairs and inability to lie flat at night. A recent echocardiogram shows normal LV size and function with an LVEF of 65%. She has mild mitral regurgitation, a dilated left atrium and her right ventricular systolic pressure is estimated at 48 mmHg. She is currently taking hydrochlorothiazide 25 mg daily and amlodipine 5 mg daily. Her blood pressure is 160/95 mmHg and heart rate is 85 bpm. On examination, her JVP is about 12 cm H_2O and there is a positive hepatojugular reflux test. The heart rate is irregular with a prominent S4. There are bibasilar crackles and 2+ pitting lower extremity edema. Electrocardiogram shows atrial fibrillation. Which of the following statements is NOT true?
   (a) Discontinuation of hydrochlorothiazide and initiation of furosemide is reasonable to relieve her congestion
   (b) Cardioversion to sinus rhythm should be considered to reduce her HF symptoms
   (c) Addition of lisinopril and titration to reduce her blood pressure into the normal range will provide long-term symptomatic benefit
   (d) A beta-blocker should be added to reduce the incidence of sudden cardiac death

4. A 62 year old man with a chronic non-ischemic cardiomyopathy is admitted for a HF exacerbation. This is his fourth admission in the last year. He has dyspnea with minimal activity and is unable to leave his home. His blood pressure is 95/40 mmHg and heart rate is 98 bpm. Examination shows a jugular venous pressure of 10 cm H20, clear lung fields, a regular rate with a third heart sound, and a tricuspid regurgitation murmur. His abdomen is distended and he has cool extremities with 1+ lower extremity edema. Right heart catheterization shows a pulmonary capillary wedge pressure of 25 mmHg, with a mean pulmonary arterial pressure of 40 mmHg. The CO is 3.0 L/min. His PVR is 5 Wood Units, and there is no change with administration of sodium nitroprusside or inhaled nitric oxide. At this time, all of the following are appropriate EXCEPT:
   (a) Palliative care consultation
   (b) Initiation of intravenous inotrope
   (c) Consideration of LVAD placement
   (d) Cardiac transplantation

ANSWERS

1. (c) Beta-blockers and ACE-inhibitors have a Class I indication in the treatment of chronic HF due to LV systolic dysfunction. These medications should be titrated to maximally tolerated levels to achieve their full benefit on symptoms and mortality. The addition of an angiotensin-receptor blocker to therapy with an ACE-inhibitor has been shown to reduce hospitalizations but not to improve survival. This combination should be used with caution when there is significant renal failure. Spironolactone should not be used in women with a serum creatinine >2.0 mg/dL. A cardiac resynchronization device is only indicated in patients on optimal medical therapy who have a QRS width >120 ms. Digoxin is approved for the treatment of symptoms in chronic HF but has no effect on mortality.

2. (a) Digoxin is a useful agent for the management of atrial fibrillation in patients with LV systolic dysfunction. It works at the atrioventricular node to slow conduction and reduce the ventricular response to atrial fibrillation. Digoxin has also been shown to reduce hospitalizations in patients with chronic HF. Amiodarone is also a useful agent for the management of atrial fibrillation in chronic HF; however, sotalol is relatively contraindicated in patients with a low LVEF due to its negative inotropic properties. No studies have demonstrated a mortality benefit to the maintenance of sinus rhythm in heart failure, although it may provide symptom relief. Calcium-channel blockers should not be used in LV systolic dysfunction due to their negative inotropy.

3. (d) No medical therapies have been shown to produce a survival benefit in the management of HFpEF. Goals of therapy include reduction of congestion and control of blood pressure. Due to stiff ventricles, HFpEF patients tend to have more symptoms in atrial fibrillation and often benefit from maintenance of sinus rhythm.

4. (d) This patient has advanced HF (AHA Stage D) with low cardiac output and recurrent hospitalizations. He should be considered for advanced therapies. Cardiac transplantation would be a consideration if his PVR was lower. However, a PVR >4.0 Wood Units is an absolute contraindication to transplantation. If an elevated PVR can be lowered with medications, these patients may be considered for transplant. In this case, the patient did not respond to an attempt at vasodilator therapies during his right heart catheterization. In some cases, PVR may come down following LVAD implantation. It is not possible to know if that will be the case with this patient. Palliative care, continuous inotropic infusions, and LVADs are all potential options for the treatment of advanced HF.

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CHAPTER 26

TIMOTHY W. CHURCHILL, AARON L. BAGGISH, AND RORY B. WEINER

Cardiomyopathies: Dilated, Restrictive/Infiltrative, and Hypertrophic Cardiomyopathies

CHAPTER OUTLINE

ABBREVIATIONS

AC	Arrhythmogenic cardiomyopathy
ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
AR	Aortic regurgitation
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor nephrilysin inhibitor
ARVC	Arrhythmogenic right ventricular cardiomyopathy
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CMV	Cytomegalovirus
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CXR	Chest x-ray
DCM	Dilated cardiomyopathy
E′	Early peak diastolic tissue velocity
ECG	Electrocardiogram
HCM	Hypertrophic cardiomyopathy
HIV	Human immunodeficiency virus
ICD	Implantable cardioverter defibrillator
LV	Left ventricle or left ventricular
LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
RV	Right ventricle or right ventricular
RVEDP	Right ventricular end-diastolic pressure
RVSP	Right ventricular systolic pressure
SAM	Systolic anterior motion
SCD	Sudden cardiac death
SPEP	Serum protein electrophoresis

QUICK REVIEW

- The dilated cardiomyopathies are a diverse set of conditions with wide-ranging etiologies and represent the most common indication for heart transplantation. A focused history and careful laboratory and imaging evaluation is essential, with a particular focus on the identification of reversible causes.
- The central feature of restrictive cardiomyopathies is a pattern of impaired ventricular filling due to decreased compliance, and signs and symptoms of right-sided heart failure tend to dominate the clinical picture.
- Distinction between restrictive and constrictive cardiomyopathies is an important clinical challenge. Important features that suggestive constrictive physiology include findings from *clinical evaluation* (prior cardiac surgery, +Kussmaul's sign), *imaging* (increased early diastolic tissue Dopplers (E′), a septal bounce, exaggerated respiratory variation of mitral inflows, and pericardial thickening on cross-sectional imaging), and *catheterization* (equalization of RV and LV diastolic pressures, modest elevation of the RVSP (typically <55 mmHg), and discordance of RV and LV pressures with respiration).
- Hypertrophic cardiomyopathy (HCM) is a common genetic disease characterized by marked left ventricular hypertrophy in the absence of a clear hemodynamic stimulus. LV morphology varies significantly, with common variants including septal predominant (often obstructive) and apical predominant.
- The primary clinical concern in HCM is the risk of sudden cardiac death. Guidelines suggest consideration of primary prevention ICD therapy based on five criteria, although emerging risk factors have been identified including left ventriculatr left ventricular aneurysm.
- Medical therapy in HCM is directed at alleviation of patients' symptoms by reducing contractile force (using β-blockers, calcium channel blockers, or disopyramide) and thereby decreasing left ventricular outflow tract. In patients with LVOT obstruction who remain symptomatic despite medical therapy, septal reduction therapy with surgical myectomy or alcohol septal ablation may be considered.

DCM

Definition

- Ventricular dilation and impaired contractility (left ventricle [LV] and/or right ventricle [RV]); typically normal LV wall thickness
- Prevalence 1:2500. Common features of DCM and other cardiomyopathies are described in Table 26-1.

TABLE 26-1

TYPICAL FEATURES OF THE VARIOUS FORMS OF CARDIOMYOPATHY

PARAMETER	DCM	RESTRICTIVE/ INFILTRATIVE	HCM
Definition	Ventricular dilation/ impaired contractility	Impaired ventricular filling due to decreased compliance	Marked LVH in the absence of a pressure load
Common causes	CAD Valve disease Idiopathic Familial Infectious Toxin	Myocardial infiltration (amyloid, sarcoid, hemochromatosis) Endomycardial (Löeffler′s endocarditis)	Familial Sporadic
Classic echocardiographic findings	Ventricular dilation ± thrombus ↓ LVEF MR	↑ Wall thickness Biatrial enlargement	LVH (asymmetric) SAM LVOT gradient

Etiology [1]

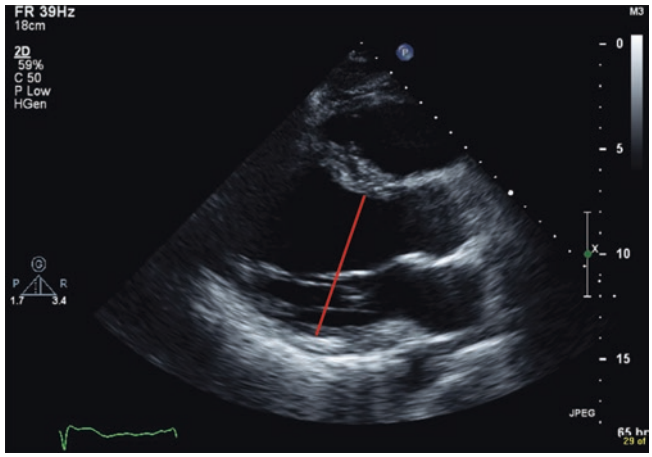
- Cardiac causes: Ischemia/coronary artery disease (CAD); valvular heart disease (i.e. chronic volume overload from aortic regurgitation [AR] or mitral regurgitation [MR])
- Idiopathic: Potentially undiagnosed genetic mutations or infectious causes
- Familial (20–35% of DCM): Mutations in contractile sarcomeric (i.e. titin), nuclear envelop (Lamin A/C), and transcriptional coactivator proteins
  - Defined as DCM of unknown cause in 2 or more closely related family members
- Infectious
  - Viral (i.e. Coxsackie, Adenovirus, cytomegalovirus [CMV], human immunodeficiency virus [HIV])
  - Bacterial (i.e. Lyme), Fungal, Parasitic (Chagas disease, frequently LV apical aneurysm)
- Toxic
  - Alcohol, cocaine
  - Chemotherapeutic agents: Anthracyclines (increased risk with dose >550 mg/m^2), cyclophosphamide, trastuzumab
- Tachycardia-mediated: Proportional to heart rate and duration of tachycardia
- Premature ventricular contraction (PVC)-Induced: Requires high burden of PVCs (variably defined, typically >10–15%)
- Stress-induced (Takotsubo): Classically apical ballooning (other variants possible); most commonly post-menopausal women in response to psychological or physiological stressor
- LV noncompaction: Prominent trabeculations, particularly in LV apex
- Infiltrative cardiomyopathy: Can present as a mix of DCM and restrictive cardiomyopathy; LV systolic dysfunction more common in late-stage disease.
- Arrhythmogenic right ventricular cardiomyopathy (ARVC—also referred to as Arrhythmogenic Cardiomyopathy or AC): Fibrofatty tissue replacement, can also involve the LV
- Metabolic: Hypothyroidism, pheochromocytoma, acromegaly, thiamine deficiency
- Peripartum: Final month of pregnancy to first 5 months after delivery
- Autoimmune
  - Collagen vascular disease (i.e. systemic lupus erythematosus, scleroderma, polymyositis, rheumatoid arthritis, polyarteritis nodosa)
  - Idiopathic giant cell myocarditis: Can be fulminant in presentation; arrhythmia is a prominent feature
  - Eosinophilic: Hypersensitivity (mild) or acute necrotizing (severe)

History/Physical Examination and Diagnostic Evaluation

- Chest pain with certain etiologies (coronary artery disease, myocarditis)
- Focused history of alcohol or drug use, current or past exposure to chemotherapy, and the ability of the patient to perform daily activities.
- Careful family history for ≥3 generations
- Symptoms and signs of left and/or right-sided heart failure (dyspnea, orthopnea, jugular venous distention, lower extremity edema)
- Diffuse and laterally displaced point of maximal impulse, S3 gallop, murmur (i.e. MR)
- *Initial diagnostic evaluation*
  - 12-lead electrocardiogram (ECG): Evaluate for poor R wave progression, Q waves, left atrial enlargement, bundle branch block, atrial fibrillation (AF)
  - Chest x-ray (CXR): Increased cardiac silhouette, pleural effusions, Kerley B lines

FIGURE 26-1

Transthoracic echocardiogram from a patient with DCM (parasternal long-axis view) demonstrating LV dilation (red line shows the increased LV inner dimension at end-diastole)



- Transthoracic echocardiogram (Fig. 26-1): LV dilation, decreased LV ejection fraction (LVEF), global or regional LV hypokinesis, MR (papillary muscle displacement and incomplete mitral valve closure), RV dilation and hypokinesis, LV thrombus
- Laboratory studies: Complete blood count, serum electrolytes, blood urea nitrogen and serum creatinine, fasting blood glucose or hemoglobin A1C, urinalysis, lipid profile, liver function tests, and thyroid-stimulating hormone.
- Measurement of natriuretic peptides (BNP and NT-proBNP) can be useful in the urgent care setting in patients in whom the diagnosis of heart failure is uncertain (Class I, Level of Evidence A for assessment of dyspnea in ambulatory patient with uncertain diagnosis) [2].

■ *Disease-specific evaluation*

- Ischemic (CAD):
  - ■ Stress test: standard SPECT imaging less reliable due to false positive and false negative results. Uncertain if PET imaging offers advantages at this time.
  - ■ Coronary computed tomography (CT) angiogram: Most useful when low pre-test probability
    - Coronary angiography—Reasonable when ischemia may be contributing to heart failure (Class IIa, Level of Evidence C) [2]
      - ■ Patients with stable ischemic heart disease who develop signs and symptoms of heart failure should be evaluated to determine whether coronary angiography should be performed (Class I, Level of Evidence B) [3]
      - ■ Coronary angiography termed "Appropriate" for evaluation of newly diagnosed systolic heart failure [4]
- Cardiac magnetic resonance imaging (MRI): Useful in evaluation of myocarditis or infiltrative disease; offers data on myocardial viability based on late gadolinium enhancement
- Iron studies, anti-nuclear antibody (ANA), serum protein electrophoresis (SPEP), HIV, selenium, thiamine, etc. based on clinical suspicion for specific causes

■ Endomyocardial biopsy [5]

- New-onset heart failure of <2 weeks' duration with hemodynamic compromise suggesting severe myocarditis eligible for steroid treatment (Class I, Level of Evidence B)
- New-onset heart failure of 2 weeks to 3 months duration and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 weeks (Class I, Level of Evidence B)
- Should not be performed as a part of routine evaluation (Class III, Level of Evidence C) [2]

Treatment and Prognosis

- Identification and treatment of underlying cause if possible
- See Chap. 25 (Chronic and End-Stage Heart Failure) for detailed treatment including medical therapy (β-blocker, angiotensin converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB], angiotensin receptor-neprilysin inhibitor [ARNI], aldosterone antagonist), device therapy (implantable cardioverter defibrillator [ICD], cardiac resynchronization therapy [CRT])
- Consideration of reversibility is needed before implantation of device therapy
- Immunosuppression for giant cell myocarditis, eosinophilic disease, and collagen vascular disease
- Prognosis depends on etiology, worst for ischemic cardiomyopathy [1]; overall, DCM most frequent cause of heart transplantation
- Screening of family members for familial DCM (after other more common causes, i.e. CAD, cardiotoxic agents, etc.) have been excluded [6]
  - Genetic testing should be considered for the most clearly affected person (proband) in a family to facilitate cascade family screening and management
  - Clinical screening (history, physical exam, ECG, echocardiogram) for DCM in asymptomatic first degree relatives is recommended; interval of screening depends on genotype status
  - Genetic and family counseling is recommended for all patients and families with familial DCM

RESTRICTIVE AND INFILTRATIVE CARDIOMYOPATHY

Definition

- Impaired ventricular filling (restrictive filling) due to decreased compliance in the absence of pericardial disease
- Normal or decreased volume of both ventricles associated with biatrial enlargement; normal or increased LV wall thickness. Common features of restrictive / infiltrative and other cardiomyopathies are described in Table 26-1.

Etiology [7]

Myocardial

- Infiltrative
  - Amyloidosis [8]: Primary (AL), familial (transthyretin), senile; more common in males, average age of presentation approximately 60 years
    - Evaluate for systemic signs and symptoms (nephrotic syndrome, peripheral neuropathy, carpal tunnel, macroglossia, etc.).
  - Sarcoidosis: conduction abnormalities, arrhythmia (i.e. ventricular tachycardia); clinical evidence of myocardial involvement in ~5% of patients with systemic sarcoidosis (20–30% show cardiac involvement at autopsy) [9]
  - Hemochromatosis: Liver function abnormalities, diabetes, skin hyperpigmentation
- Storage diseases: Gaucher's, Fabry's (neuropathic pain, impaired sweating, skin rashes; can mimic HCM), Hurler's, glycogen storage disease
- Autoimmune (scleroderma, polymyositis-dermatomyositis)
- Diabetes mellitus
- Friedrich's ataxia (gait abnormalities)
- Idiopathic

Endomyocardial

- Löeffler's endocarditis (hypereosinophilic syndrome): Temperate climates, mural thrombi that have embolic potential
- Endomyocardial fibrosis: Tropical regions (Africa), variable eosinophil levels
  - Bimodal incidence peak at ages 10 and 30
  - Echocardiography shows apical fibrosis of LV and/or RV, giant atria, restrictive Doppler filling pattern on mitral inflow (similar findings can be seen in Loeffler's, which may also have localized thickening of the posterobasal LV wall)
- Radiation
- Serotonin: Carcinoid, ergot alkaloids, serotonin agonists

History/Physical Examination and Diagnostic Evaluation

- Right > left-sided heart failure
- Peripheral edema refractory to diuretics
- Tachyarrhythmias (i.e. ventricular tachycardia)
- Thromboembolic complications
- Increased jugular venous pressure with hepatojugular reflux; S4 ± S3
- Edema: Sacral, ascites, lower extremity edema
- 12-lead ECG: Low-voltage in amyloidosis, pseudoinfarct pattern (Q waves), arrhythmia (atrial or ventricular), conduction abnormalities
- CXR: Normal size cardiac silhouette, atrial enlargement
- Transthoracic echocardiogram
  - Increased wall thickness
  - Bi-atrial enlargement
  - Mitral and tricuspid regurgitation
  - Short trans-mitral Doppler deceleration time (<160 ms)
  - Reduced early peak diastolic tissue (E′) Doppler velocity (<10 cm/s)
- Echocardiographic features of specific disease states:
  - Amyloid (Fig. 26-2): Granular myocardial texture, biventricular wall thickening, atrial enlargement, valve thickening, small pericardial effusion
  - Sarcoid: Basal septal wall motion abnormality

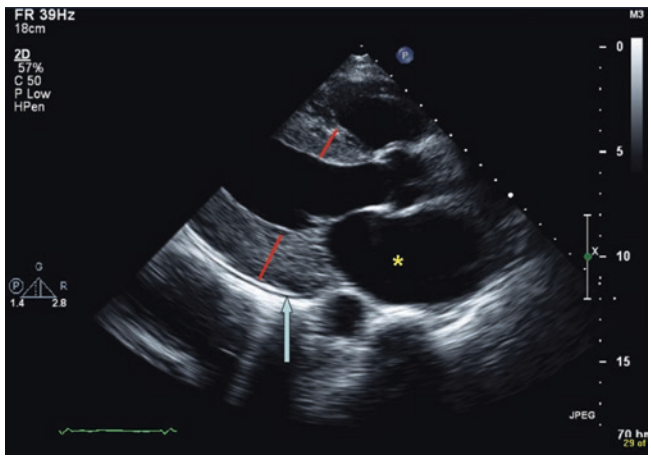


FIGURE 26-2

Transthoracic echocardiogram from a patient with amyloidosis (parasternal long-axis view) demonstrating increased wall thickness (red lines), left atrial enlargement (yellow asterick), and a trace pericardial effusion (blue arrow)

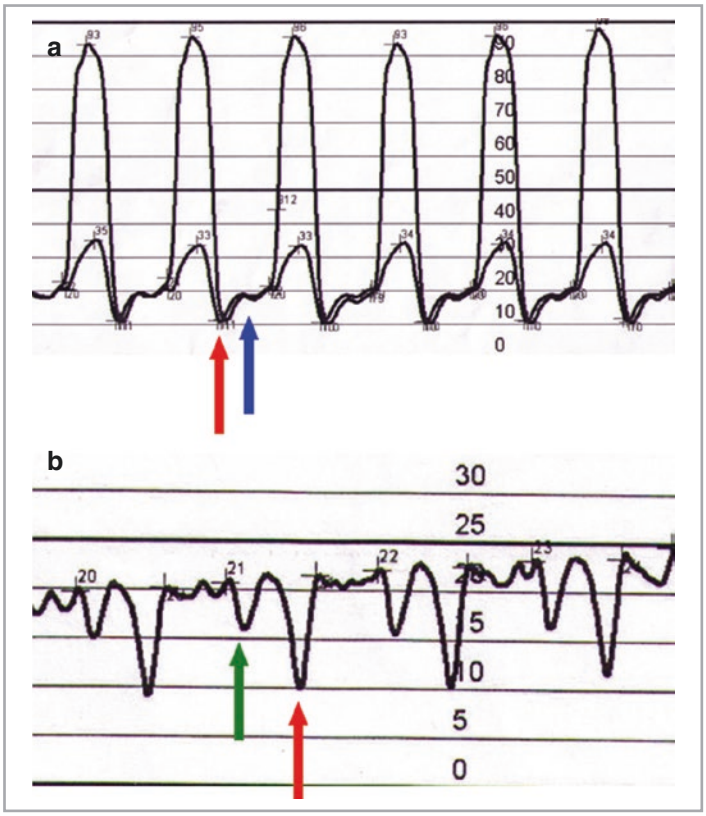


FIGURE 26-3

Hemodynamic pressure tracings obtained at cardiac catheterization in a patient with restrictive cardiomyopathy. (**a**) The characteristic hemodynamic feature of restrictive cardiomyopathy (as well as constrictive pericarditis) is a deep and rapid decline in ventricular pressure at the onset of diastole (red arrow), with a rapid rise to a plateau in early diastole (blue arrow). This dip and plateau is referred to as the *square root sign*. (**b**) Right atrial pressure tracing showing a prominent y descent (red arrow) followed by a rapid rise and plateau. The x descent is also rapid (green arrow). The combination results in the M or W waveform

- Cardiac MRI: Late gadolinium enhancement pattern
  - Amyloidosis: Diffuse throughout both ventricles, particularly the subendocardium
  - Sarocoidosis: Patchy, basal and lateral LV walls
- Cardiac PET: Assess active inflammation in cardiac sarcoidosis; can be used to guide treatment
- Technetium (Tc-99m) pyrophosphate (PYP) nuclear imaging sensitive and specific for transthyretin amyloidosis if markedly positive [10]. Mild positivity may be seen in AL amyloid.
- Cardiac catheterization for hemodynamic evaluation
  - Dip and plateau (square root sign) in the ventricular pressure tracing (Fig. 26-3a): Deep and rapid early decline in ventricular pressure at the onset of diastole, with a rapid rise to a plateau in early diastole
  - The dip and plateau manifests in the atrial pressure tracing as a prominent y descent followed by a rapid rise and plateau. The x descent may also be rapid. The combination results in the M or W characteristic waveform in the atrial pressure tracing (Fig. 26-3b)
  - Square root sign and M or W pattern are typical for restriction, but are also characteristic of pericardial constriction. Differentiating features of restrictive cardiomyopathy and constrictive pericarditis are highlighted in Table 26-2.
- Endomyocardial biopsy: Heart failure with unexplained restrictive cardiomyopathy (Class IIa, Level of Evidence C) [5]
  - Specific for ruling out certain diseases (i.e. amyloidosis)
  - Biopsy considerably less-sensitive for sarcoidosis given patchy nature of myocardial involvement

TABLE 26-2

FEATURES OF RESTRICTIVE CARDIOMYOPATHY COMPARED WITH CONSTRICTIVE PERICARDITIS

FEATURE	RESTRICTION	CONSTRICTION
Physical exam	± Kussmaul's sign Powerful PMI Murmurs of MR or TR	+ Kussmaul's sign Absent PMI + Pericardial knock
Echocardiogram	Increased wall thickness Biatrial enlargement Reduced E′ MR/TR frequent *Normal* respiratory variation of mitral E velocity	Normal wall thickness Septal "bounce" Increased E′ MR/TR infrequent *Exaggerated* respiratory variation of mitral E velocity
CT/MRI	Normal pericardium	Thick pericardium
Cardiac catheterization	LVEDP > RVEDP RVSP > 55 mmHg RVEDP < 1/3 RVSP *Concordance* of LV and RV pressure peaks with respiration	LVEDP = RVEDP RVSP < 55 mmHg RVEDP > 1/3 RVSP *Discordance* of LV an RV pressure peaks during respiration
Endomyocardial biopsy	± Specific etiology	Typically normal

LVEDP LV end-diastolic pressure, *PMI* point of maximal impulse, *RVEDP* RV end-diastolic pressure, *RVSP* RV systolic pressure, *TR* tricuspid regurgitation

Treatment and Prognosis

- Identification and treatment of underlying cause if possible
  - There is no specific treatment for idiopathic restrictive cardiomyopathy
- Heart rate control and maintenance of sinus rhythm to improve diastolic filling
- In clinical syndrome of heart failure, use of medical therapy including angiotensin converting enzyme inhibitor or angiotensin II receptor blocker and β-blocker
- Diuretics as tolerated to reduce pulmonary and systemic congestion
- Digoxin is proarrhythmic in amyloidosis and should be avoided
- Poor prognosis in symptomatic restrictive cardiomyopathy
  - 37% survival at 10 years in symptomatic idiopathic restrictive cardiomyopathy [11]
- Refractory cases may require cardiac transplantation

HCM

Definition

- Marked LV hypertrophy (LVH), typically ≥15 mm (and/or RV hypertrophy) in the absence of a hemodynamic pressure load to produce the hypertrophy. Common features of HCM and other cardiomyopathies are described in Table 26-1.
- LV morphology is variable. Common geometric variants include:
  - Concentric/non-obstructive
  - Septal predominant ± obstruction (≥1.3:1 septal to posterior wall thickness ratio)
  - Apical
  - Apical predominant
- Prevalence 0.2% (1 in 500) [12]
- Pathology characterized by myocyte fiber disarray and hypertrophy
- LV outflow tract [LVOT] obstruction can result from several factors: Hypertrophied interventricular septum, mitral valve leaflet abnormalities (typically elongation), systolic

anterior motion (SAM) of the anterior mitral valve leaflet, and abnormal papillary muscle location and attachments

- LVOT obstruction increased with decreased preload (volume depletion) or increased contractility

Etiology

- Differentiate HCM from other causes of LVH: Hypertension, aortic stenosis, athlete's heart, Fabry's disease, sarcoidosis, LV noncompaction
  - HCM versus athlete's heart
    - Most difficult to distinguish in cases of concentric LVH induced by isometric (pressure) training; less overlap with eccentric LVH induced by isotonic (volume) training
    - "Gray zone" LV wall thickness of 13–15 mm
    - Adjunctive features that favor athlete's heart: Dilated LV cavity, symmetric LVH, regression of LVH with detraining, no family history of sudden cardiac death (SCD) [13]
- HCM is 50% sporadic/gene mutation negative; 50% familial with clearly identifiable gene mutation
  - Familial: autosomal dominant mutations in cardiac sarcomere genes (i.e. β-myosin heavy chain, cardiac troponin, etc.)

History/Physical Examination and Diagnostic Evaluation

- Majority are asymptomatic
- Dyspnea: Can be the result of outflow tract obstruction, diastolic relaxation abnormalities, or MR due to SAM
- Angina: Can result from microvascular dysfunction in the absence of epicardial coronary artery disease or from concomitant CAD
- Palpitations or syncope: arrhythmia (atrial or ventricular)
- SCD: ≤1% annually [14]
  - Risk factors for SCD (Table 26-3)

TABLE 26-3

RISK FACTORS FOR SCD IN HCM

RISK FACTORS
Personal history of unexplained syncope
Family history of SCD
LV wall thickness ≥30 mm
Systolic blood pressure increase <20 mmHg with exercise
Ventricular arrhythmia on Holter monitor
Emerging risk factors[a]
Delayed gadolinium enhancement on cardiac MRI (≥15% used as a threshold) [15]
Left ventricular aneurysm [16]

[a]Emerging risk factors are supported by published data and employed in practice by some clinicians, but have not been incorporated into updated American guidelines on SCD risk stratification

- Bisferiens carotid pulse (double peak)
- Sustained point of maximal impulse
- Systolic crescendo-decrescendo murmur at the left-lower sternal border: Increased with Valsalva maneuver and standing (decreased preload)
- Apical holosystolic murmur (MR) may be present
- 12-lead ECG: Voltage criteria LVH ± ST-segment and T wave abnormalities
  - Prominent T wave inversions in leads V5–V6 suggestive of apical variant
- Transthoracic echocardiogram (Fig. 26-4)
  - Typical wall thickness ≥ 15 mm or septum to posterior wall thickness ratio ≥ 1.3:1

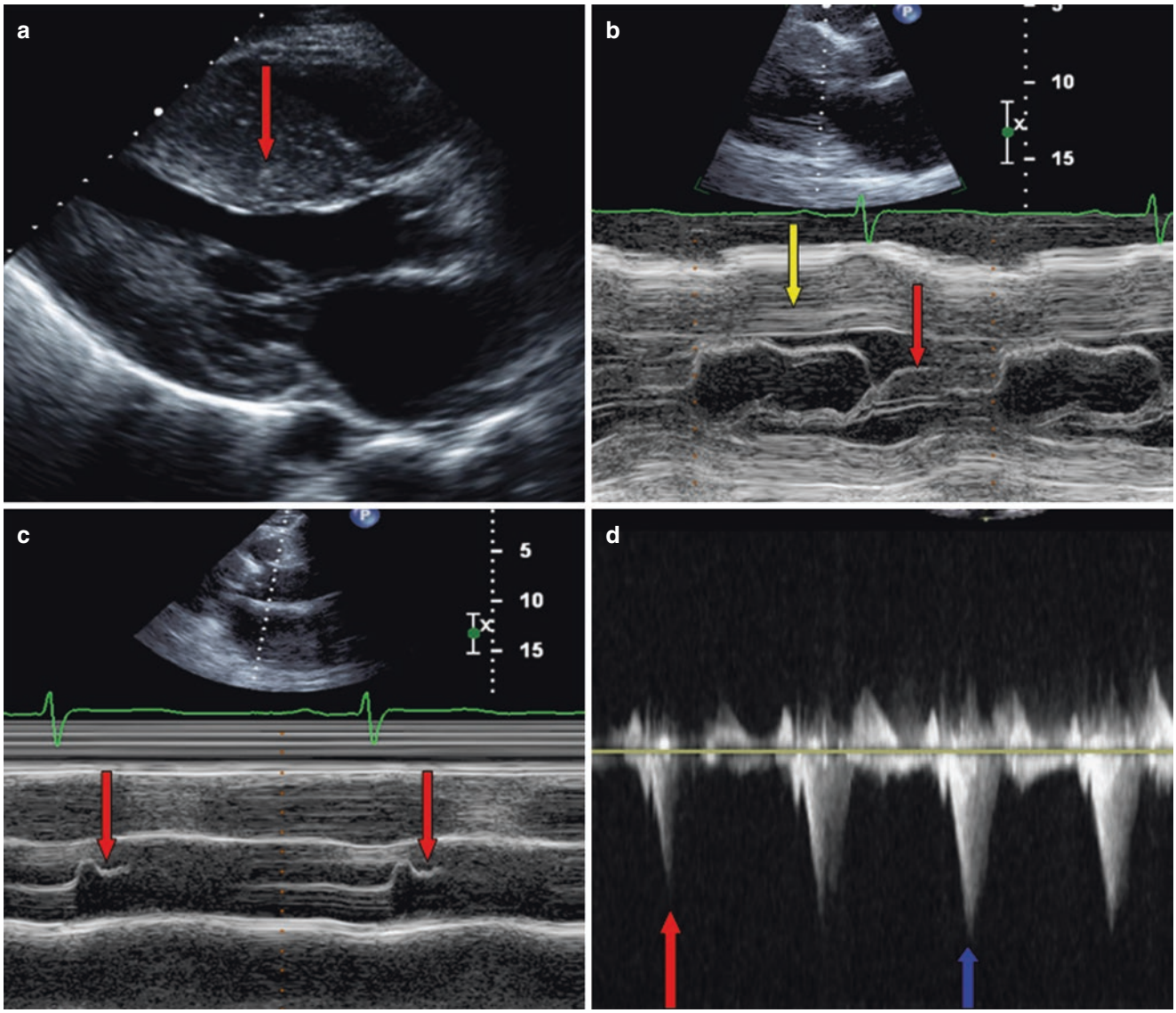


FIGURE 26-4

(**a**) Transthoracic echocardiogram from a patient with septal predominant HOCM (parasternal long-axis view) demonstrating asymmetric LVH (markedly thickened interventricular septum; red arrow). (**b**) M-mode of a parasternal long-axis view demonstrating SAM of the mitral valve (red arrow). Note the markedly thickened interventricular septum (yellow arrow). (**c**) M-mode of a parasternal long-axis view demonstrating mid-systolic closure (red arrows) of the aortic valve. (**d**) Continuous wave Doppler demonstrating a late-peaking systolic gradient in the LVOT at rest (red arrow), which is dynamic and increases with the Valsalva maneuver (blue arrow)

  - SAM and posteriorly directed MR in hypertrophic obstructive cardiomyopathy (HOCM)
  - Mid-systolic closure of the aortic valve in HOCM
  - Dynamic, late-peaking LVOT gradient (i.e. dagger shaped) in HOCM
- Stress testing: Assess blood pressure response to exercise and ischemia if symptoms of chest pain or angina equivalent; assess for arrhythmia
- Holter monitoring: Assess for subclinical ventricular arrhythmia
- Cardiac MRI: Assess for LVH and delayed hyperenhancement
  - Useful in cases of suspected HCM with equivocal echocardiograms, particularly for better visualization of LV apex
  - Subsets with LV apical aneurysm or myocardial crypts
- Cardiac catheterization
  - Coronary angiography to exclude concomitant CAD in symptomatic patients with an intermediate to high likelihood of CAD (Class I, Level of Evidence C) [17]
  - Measure LVOT pressure gradient
  - Brockenbrough sign (Brockenbrough-Braunwald-Morrow sign): Post-extrasystolic beat demonstrates decreased pulse pressure (due to increased contractility and obstruction resulting in decreased systolic pressure)

Treatment and Prognosis [17]

- Medical therapy is focused on treating symptoms (negative inotropy/chronotropy): β-blocker, verapamil and/or disopyramide
- Generally avoid vasodilators and diuretics
- Avoid digoxin
- Consider anticoagulation with warfarin in the setting of AF regardless of $CHADS_2$ score (direct acting oral anticoagulants are used frequently in clinical practice but not mentioned in 2011 guidelines)
- Competitive sport restriction [18]
  - Guidelines suggest participation in Class IA sports only (golf, billiards, bowling, cricket, curling, riflery)
- If obstructive physiology and symptoms refractory to medical therapy, consider septal reduction therapy with surgical myectomy or alcohol septal ablation in patients with prohibitive surgical risk
  - In a nonrandomized retrospective evaluation of HOCM patients <65 years old, survival free from recurrent symptoms favored myectomy over ablation (89 vs. 71%, $p = 0.01$) [19]
  - Procedural success is associated with very low mortality (<1% for myectomy; 0–4% for ablation)
  - High-grade atrioventricular block requiring permanent pacemaker can occur in 10–20% of patients undergoing septal ablation [20]
- Dual chamber pacemaker with shortened AV delay (Class IIa in symptomatic obstructive patients if pacemaker indicated for other reasons; not a first-line therapy) [17]
- ICD for SCD prevention typically considered if at least one risk factor (Table 26-3) is present [15–17]
- Family Screening [17]
  - Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM (Class I, Level of Evidence B)
  - Screening (clinical, with or without genetic testing) is recommended in first degree relatives of patients with HCM (Class I, Level of Evidence B)

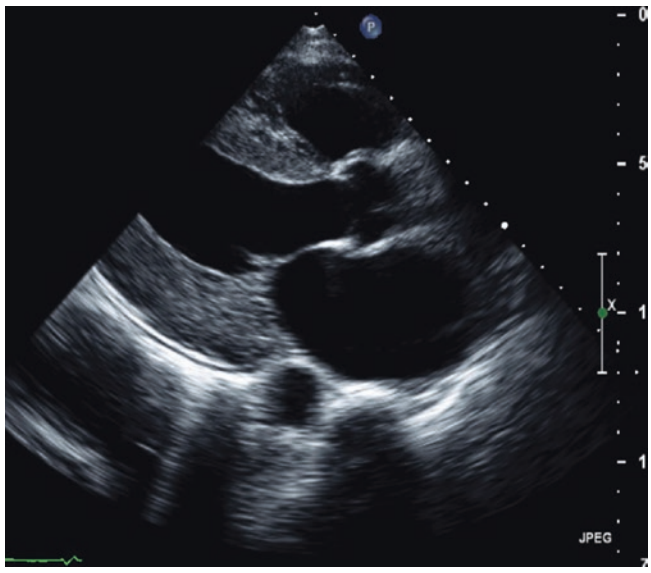
- Genetic testing is reasonable in the index patient to facilitate the identification of first degree family members at risk of developing HCM (Class IIa, Level of Evidence B)
- Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation (Class III, Level of Evidence B)
- Clinical screening: transthoracic echocardiography and ECG
  - Age < 12 years: Optional, unless symptoms, patient is a competitive athlete, or high risk features in the family
  - Age 12 to 18–21 years: Every 12–18 months
  - Age > 18–21 years: Every 5 years or at onset of symptoms (can be more frequent in families with high risk features)

Cardiomyopathies: Questions and Answers

1) A 65-year-old woman with hypertension received the news that her husband died suddenly and unexpectedly after a myocardial infarction. Later that day she developed chest pain and dyspnea. The next day she presents to the local emergency department. On examination, her temperature is 37.2 °C, blood pressure 95/60 mmHg, heart rate 110 bpm, respiratory rate 18/min and O_2 saturation 95% on room air. There is no jugular venous pressure elevation and lungs are clear on exam. CBC, electrolytes and renal function are normal and troponin T is elevated at 0.23 ng/mL. ECG shows normal sinus rhythm with anterior ST-segment elevation and she undergoes emergent coronary angiography which shows no obstructive epicardial coronary artery disease. Left ventriculography shows systolic apical ballooning of the LV with moderately impaired LV systolic function. She is admitted to the telemetry unit and that night is persistently hypotensive (SBP <90 mmHg) and tachycardic and is transferred to the cardiac intensive care unit. A crescendo—decrescendo systolic murmur is auscultated and a transthoracic echocardiogram shows LVEF 40%, apical wall motion abnormality and systolic anterior motion of the mitral valve. The next best step in management is:
   a. Administration of intravenous inotropic medication
   b. Placement of an intra-aortic balloon pump (IABP)
   c. Administration intravenous fluids and cautious initiation of beta blockade
   d. Repeat coronary angiography

   Answer C. This scenario depicts a woman with stress (Takotsubo) cardiomyopathy. This is a syndrome characterized by transient regional systolic dysfunction of the LV, mimicking myocardial infarction, but in the absence of angiographic evidence of obstructive coronary artery disease or acute plaque rupture. Stress cardiomyopathy was first described in 1990 in Japan and has since been increasingly recognized all over the world. The term "takotsubo" refers to the Japanese name for an octopus trap, which has a shape similar to the systolic apical ballooning appearance of the LV in the most common form of this disorder (where mid and apical segments of the LV are depressed, and there is hyperkinesis of the basal walls). The onset of stress cardiomyopathy is frequently but not always triggered by intense emotional or physical stress (i.e., death of relatives, natural disasters or acute medical illness). Approximately 10% of patients with stress cardiomyopathy develop cardiogenic shock, which may or may not correlate with the extent of LV systolic dysfunction. One explanation for discordance between ventricular dysfunction and risk of shock is the presence of LVOT obstruction, which has been described in up to 25% of patients with stress cardiomyopathy. Hypotension/shock associated with moderate or severe LVOT obstruction should **not** be treated with inotropic agents, as they can worsen the degree of obstruction. The recommended approach to patients with stress cardiomyopathy with moderate to severe LVOT obstruction includes increasing pre-load with intravenous fluids (in the absence of significant pulmonary congestion) and the use of beta blockers. In patients with LVOT obstruction and severe hypotension that does not respond to initial medical therapy and volume resuscitation, an IABP can be placed. In this patient, there is no clinical reason to suspect acute plaque rupture since the time of initial angiography so repeat coronary angiography is not indicated.

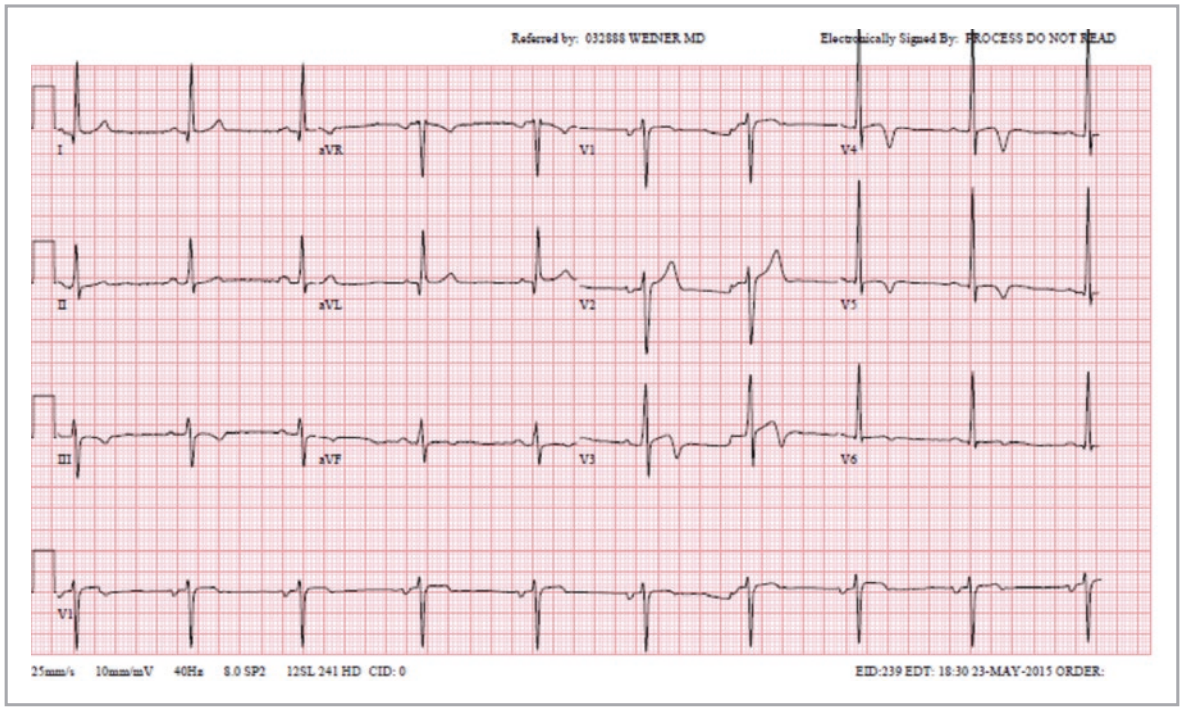
2) A 62-year-old man developed several months of increasing dyspnea and lower extremity edema. He reports positional lightheadedness (lightheaded when standing). He feels fatigued in general and can no longer go for walks for exercise. He reports numbness and tingling in his extremities. He presents to his primary physician and physical examination reveals temperature 37.0 °C, blood pressure 105/60 mmHg, heart rate 85 bpm, respiratory rate 16 min and O_2 saturation 97% on room air. There is jugular venous pressure elevation and evidence of ascites and 2+ lower extremity edema. CBC is normal and renal function shows creatinine 1.3 mg/dL. ECG shows normal sinus rhythm with low voltage in the limb leads. A transthoracic echocardiogram is performed and a representative parasternal long axis view is shown here:



The most appropriate first step to confirm the diagnosis is:
a. Exercise treadmill test
b. Cardiac magnetic resonance imaging
c. Serum free kappa and lambda light chains
d. Endomyocardial right ventricular biopsy
e. Abdominal fat pad biopsy

Answer E. Cardiac amyloidosis should be considered in adults with new onset and unexplained heart failure and an echocardiogram showing increased wall thickness with a non-dilated LV cavity, particularly when associated with low voltage on ECG. While certain cardiac magnetic resonance (CMR) findings are helpful in supporting the diagnosis of all forms of amyloid cardiomyopathy, a definitive diagnosis requires tissue confirmation. The diagnosis of cardiac amyloidosis is confirmed either by demonstrating amyloid deposits on endomyocardial biopsy or, in patients with typical cardiac findings, by demonstrating amyloid deposits on histologic examination of a biopsy from more accessible other tissues (i.e. abdominal fat pad). Subcutaneous fat pad aspiration, which would be an appropriate first step in this patient to confirm the diagnosis, may show amyloid deposits in more than 80% of patients, although experience in staining the small deposits is necessary to avoid false-positive or false-negative results. If a patient has a typical noninvasive appearance of cardiac amyloidosis and a positive biopsy for amyloid from a non-cardiac site, there is no absolute need to pursue an endomyocardial biopsy. If biopsy from other sites is inconclusive, endomyocardial biopsy is almost universally positive in cardiac amyloidosis, unlike many other cardiomyopathies. In skilled hands, the procedure carries a low complication rate. Measurement of serum free kappa and lambda light chains demonstrates an excess of either kappa or lambda in greater than 90% of cases of AL amyloidosis and is a very useful test for monitoring response to therapy. Exercise testing would not be useful in establishing the diagnosis in this case.

3) A 20-year-old male basketball player has palpitations and near syncope during a basketball game. He has no personal history of prior exertional syncope or a family history of sudden cardiac death. A 12-lead electrocardiogram (ECG) performed as part of his evaluation is shown here.



He then undergoes a transthoracic echocardiogram which shows asymmetric left ventricular hypertrophy (LVH) with an interventricular septal thickness of 19 mm. All of the following are accepted risk factors for sudden cardiac death (SCD) in this condition and would favor implantation of an implantable cardioverter defibrillator, except:
a. Prior cardiac arrest or sustained ventricular tachycardia
b. Family history of sudden cardiac death in a first degree relative
c. Personal history of unexplained syncope
d. Maximum left ventricular wall thickness ≥30 mm
e. Presence of late gadolinium enhancement on cardiac magnetic resonance imaging

Answer E. Hypertrophic cardiomyopathy (HCM) is a genetic heart muscle disease caused by mutations in one of several sarcomere genes that encode components of the contractile apparatus of the heart. HCM is characterized by left ventricular hypertrophy (LVH) of various morphologies. HCM is the leading cause of death in young athletes in the United States. ICD is recommended in patients with HCM and prior cardiac arrest or ventricular arrhythmia (Class I recommendation). The presence of a personal history of unexplained syncope, family history of SCD caused by HCM in first degree relatives or massive LVH (LV wall thickness ≥ 30 mm) are reasonable indications for an ICD (Class IIA). Systolic blood pressure increase < 20 mmHg of exercise and ventricular arrhythmia on ambulatory monitor may favor ICD

placement in the presence of other risk factors. More recently, the presence of a left ventricular (LV) apical aneurysm has been identified as a high-risk feature that increases the risk of life-threatening ventricular tachycardia and may be an indication for an ICD. Additionally, late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging is common in HCM and appears to reflect fibrosis, which has been proposed as a potential pathogenic factor for arrhythmia. In patients with one risk marker, but in whom high-risk status remains uncertain, the results of contrast-enhanced cardiac magnetic resonance (CMR) imaging can aid in resolving high-risk status and the need for primary prevention ICD therapy. As a stand-alone risk factor, LGE on CMR is not universally accepted as an indication for ICD, although it may be considered if there is extensive LGE.

4) A 34-year-old man who previously immigrated from South America presents with difficulty swallowing. He also reports palpitations and ambulatory monitoring reveals non-sustained ventricular tachycardia. He therefore has a transthoracic echocardiogram (TTE). The image below shows the TTE apical 4-chamber view with contrast administration to better delineate the borders of the left ventricular apex. Which of the following is true regarding this diagnosis?
   a. It is caused by a previous viral infection
   b. It is part of an inherited familial syndrome
   c. It is caused by infection with Tyrpanosoma cruzi
   d. It is the result of iron overload

   Answer C. A left ventricular (LV) apical aneurysm, as seen in the TTE image, is a manifestation of Chagas cardiomyopathy. Chagas disease is caused by infection with the protozoan Trypanosoma cruzi. The disease is prevalent in Central and South America. The major cardiovascular manifestation is an extensive myocarditis that typically becomes evident years after the initial infection. Ten to 15% of asymptomatic patients have evidence of apical aneurysm on echocardiography. The echocardiographic findings in advanced disease included dilated cardiomyopathy with reduced ejection fraction and increased end-diastolic and end-systolic volumes. The right ventricle can also be involved.

   Viral cardiomyopathy as a result of infection with viruses such as Coxsackie virus can result in dilated cardiomyopathy but does not classically cause an LV apical aneurysm. Familial dilated cardiomyopathy is another cause of cardiomyopathy, but does not classically cause LV apical aneurysm. Iron overload, secondary to hemochromatosis, can cause a dilated or restrictive cardiomyopathy, and is classically associated with bronze skin and diabetes mellitus.

5) Differentiation of pericardial constriction and restrictive cardiomyopathy has important treatment implications. The following are all typical features of restrictive cardiomyopathy, except:
   a. Discordance of LV and RV pressure peaks with respiration
   b. Increased wall thickness on echocardiography
   c. Pulmonary hypertension
   d. Normal pericardium on CT or MRI

   Answer A. At cardiac catheterization, restrictive cardiomyopathy shows concordance of LV and RV pressure peaks with respiration. In contrast, pericardial constriction shows discordance of LV and RV pressure peaks during respiration. The discordance in pericardial constriction results from a dissociation of intrathoracic and intracardiac pressures and is a sign of ventricular interdependence. Distinguishing features of restriction versus constriction are shown in Table 26-2 of this chapter.

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CHAPTER 27

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Myocarditis and Inflammatory Cardiomyopathy

CHAPTER OUTLINE

ABBREVIATIONS

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
AHA	American Heart Association
ANEM	Acute necrotizing eosinophilic myocarditis
ARB	Angiotensin II receptor blocker
AV	Atrioventricular
CMR	Cardiac magnetic resonance imaging
DCM	Dilated cardiomyopathy
ECMO	Extracorporeal membrane oxygenation
EKG	Electrocardiogram
HAART	Highly active anti-retroviral therapy
HCV	Hepatitis C virus
HF	Heart failure
HHV6	Human herpes virus 6
HIV	Human immunodeficiency virus
IABP	Intra-aortic balloon pump
ISFC	International Society and Federation of Cardiology
LGE	Late gadolinium enhancement
LV	Left ventricle
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
PCR	Polymerase chain reaction
STEMI	ST-elevation myocardial infarction
VT	Ventricular tachycardia
WHO	World Health Organization

INTRODUCTION AND DEFINITION

- There is no individual ACC/AHA guideline on myocarditis, though there are comments on myocarditis in the ACC/AHA 2013 Guideline for the Management of Heart Failure [1] and the Heart Failure Society of America 2010 Heart Failure Guidelines [2]. The most comprehensive update on myocarditis is from the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) definition [3].

- **Myocarditis** is an inflammatory disease of the myocardium, based on histological, immunological, and immunohistochemical criteria.
- **Inflammatory cardiomyopathy** is specific term referring to myocarditis accompanied by cardiac dysfunction (thus there are histological and functional elements of this definition). However, the broader term myocarditis in common use typically encapsulates this subset as well.
- In contrast, dilated cardiomyopathy (DCM) is a clinical diagnosis based on ventricular structure and function. Thus, myocarditis/inflammatory cardiomyopathy and DCM are not mutually exclusive.
  - Inflammation of the myocardium may cause HF in about 10% of cases of initially unexplained cardiomyopathy.

- Histological, immunological, and immunohistochemical criteria for defining myocarditis:
  - Histological (Dallas criteria) [4]: active inflammatory cellular infiltrate within the myocardium and associated myocyte necrosis
    - Active myocarditis: an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease
    - Borderline myocarditis: when the inflammatory infiltrate is too sparse or myocyte injury is not demonstrated
    - Subtypes are based on type of inflammatory cell infiltrate (Table 27-1 and Fig. 27-1): while the infiltrate is lymphocytic in more than 90% of myocarditis cases, eosinophilic infiltration or giant cell formation may occasionally be seen.
    - The histologic differentiation of myocarditis from idiopathic DCMs remains nebulous and under investigation.
  - Immunological
  - Immunohistochemical [5]: based on certain abnormal amounts of leukocytes, monocytes, and lymphocytes infiltrating the myocardium.

INCIDENCE AND NATURAL HISTORY

- True incidence of myocarditis in the general population is unknown due to heterogeneity of clinical presentations, and the fact that the gold standard for diagnosis has been endomyocardial biopsy. Estimates derive from published trials and large case series.
  - From the US Myocarditis Treatment Trial, approximately 10% of patients with recent-onset dilated cardiomyopathy met histologic criteria for myocarditis [6].
- Natural history varies with underlying etiology and presenting symptoms.
- For most adults with acute dilated cardiomyopathy due to myocarditis, ventricular function and clinical status typically improves with standard heart failure (HF) treatment, however, transition of acute myocarditis to dilated cardiomyopathy is seen in approximately 10–20% of patients [7], despite appropriate immunosuppression therapy. This may be more common in histologically confirmed chronic inflammation.
- 5-year survival in acute myocarditis is about 60% and is comparable to survival in patients with idiopathic dilated cardiomyopathy (DCM) without myocarditis [8].
  - Survival depends primarily on myocarditis subtype and etiology: 5-year transplant free survival in giant cell myocarditis is <20%.
- Clinical findings such as syncope, bundle branch block and left ventricular ejection fraction (LVEF) < 40% at presentation have been associated with increased risk of death or cardiac transplantation in case series.

TABLE 27-1

HISTOLOGIC CLASSIFICATION OF MYOCARDITIS

HISTOLOGIC CLASSIFICATION		TIME COURSE/ SEVERITY	PRESENTATION	HISTOLOGY	TREATMENT	PROGNOSIS
Lymphocytic	Viral Autoimmune	Subclinical to fulminant	Chest pain, viral syndrome, HF	Diffuse inflammation with T cells and macrophages	Conventional HF therapy	Variable
Eosinophilic	Hypersensitivity Autoimmune	Subclinical to fulminant	Pruritic maculopapular rash and peripheral eosinophilia may be present	Infiltrates rich in macrophages and eosinophils	Conventional HF therapy, withdrawal of the offending drug, corticosteroids for systemic disease	Variable
Granulomatous	Giant cell	Fulminant	Sustained ventricular tachycardia in rapidly progressive heart failure	Diffuse infiltrate with abundant lymphocytes and scattered prominent giant cells (or presence of epithelioid granulomas in cardiac sarcoidosis)	Conventional HF therapy, potential benefit with immunosuppressants	High risk of mortality

HF heart failure

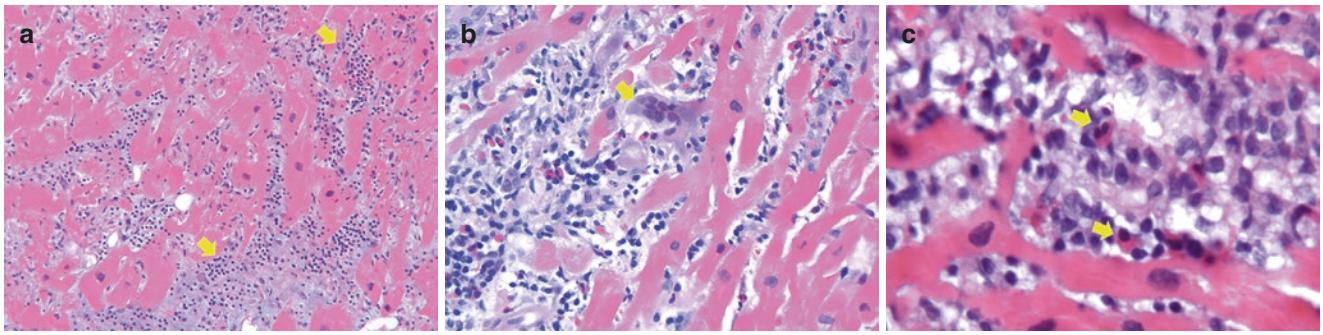

FIGURE 27-1

Histologic features of myocarditis based on hematoxylin and eosin staining. (**a**) Diffuse lymphocytic infiltrate (arrows) within myocardial fibers is often seen in lymphocytic myocarditis. (**b**) Giant cell myocarditis is characterized by diffuse heterogeneous inflammatory infiltrate with lymphocytes, eosinophils, neutrophils, plasma cells, and scattered multi-nucleated giant cells (arrow). (**c**) Mixed infiltrate with prominent number of eosinophils (arrows) are present in acute necrotizing eosinophilic myocarditis

  - Biventricular dysfunction and secondary pulmonary hypertension are other adverse predictors.
- Paradoxically, presentation with fulminant myocarditis (severe acute HF complicated by significant hemodynamic compromise and requiring inotropic or mechanical circulatory support) was classically associated with increased likelihood of recovery, if they survive the acute disease [8].
  - However, fulminant lymphocytic myocarditis patients do exhibit increased in-hospital death and need for heart transplantation, and may have a longer-term reduced LVEF compared to non-fulminant myocarditis patients [9].

CLASSIFICATION AND ETIOLOGIES (TABLE 27-1)

- Myocarditis can be classified on the basis of:
  - Histology (Table 27-1 and Fig. 27-1) and immunohistology
  - Etiologies (Table 27-2)
    - It may not be possible to always identify the etiology of myocarditis.
    - Pathogenesis involves interaction of any underlying genetic susceptibility and the inciting etiology.
  - Clinicopathologic classification and trajectories (Table 27-3)
- Specific etiologies of myocarditis
  - Giant cell myocarditis [11, 12]:
    - Rare, fatal if untreated, form of autoimmune myocarditis of unclear pathogenesis, characterized by presence of giant cells in the myocardium, in setting of multifocal infiltrate and necrosis.
    - Clinical course involves rapid deterioration in spite of conventional HF management, also high incidence of ventricular arrhythmia and advanced AV block.
    - Associated with a systemic autoimmune disorder in about 1/5 patients.
    - 89% rate of death or cardiac transplant at 5 years without treatment.
    - Patients respond favorably to multi-drug immunosuppressive regimen, improving transplant free survival to 80% in 5 years.

TABLE 27-2

SPECIFIC ETIOLOGIES OF MYOCARDITIS [5]

ETIOLOGIES	SELECTED EXAMPLES
Infectious	
Viral	Enterovirus (Coxsackie B), Adenovirus, HHV6, Parvovirus B19, HIV, HCV, influenza
Bacterial	Staphylococcus, Streptococcus, Pneumococcus, Corynebacterium, Mycobacterium
Spirochetal	*Borrelia burgdorferi*
Protozoal	*Trypansoma cruzi*, Babesia, Toxoplasma, Toxocara
Fungal	Aspergillus, Candida, Cryptococcus, Nocardia
Systemic diseases	
Autoimmune diseases	Sarcoidosis, scleroderma, lupus, hypereosinophilic syndrome, rheumatoid arthritis, Kawasaki's disease, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, celiac
Substances	
Medications	Sulfa drugs, penicillins, checkpoint inhibitors and other chemotherapeutics, thiazides, clozapine
Illicit drugs	Cocaine
Toxins	Heavy metals, arsenic
Miscellaneous	Various allergens
Miscellaneous	Radiation Insect stings

HCV hepatitis C virus, *HHV6* human herpes virus 6, *HIV* human immunodeficiency virus

TABLE 27-3

CLINICOPATHOLOGIC CLASSIFICATION OF MYOCARDITIS

CLINICO-PATHOLOGIC CLASSIFICATION [10]	ONSET	PRESENTATION	ENDOMYOCARDIAL BIOPSY FINDINGS	PROGNOSIS	RESPONSE TO IMMUNOSUPPRESSIVE THERAPY
Fulminant	Abrupt (weeks)	Cardiogenic shock (can have dilated LV with dysfunction, or non-dilated LV with thickened walls)	Multiple foci of active myocarditis	Complete recovery if survives the acute phase	Potential benefit in giant cell myocarditis, otherwise not used in general
Acute	Rapid, but less distinct than fulminant	HF with LV dysfunction ± thickened walls	Active or borderline myocarditis	Possible progression to DCM	Variable
Chronic active	Insidious	HF with LV dysfunction; frequent relapses	Active or borderline myocarditis, and mild to moderate fibrosis	DCM or restrictive cardiomyopathy	Initial response followed by relapses
Chronic persistent	Insidious	No systolic dysfunction despite persistent chest pain or palpitations	Persistent inflammation with foci of myocyte necrosis	Non-HF symptoms, normal LV function	No benefit

DCM dilated cardiomyopathy, *HF* heart failure, *LV* left ventricle

- Eosinophilic myocarditis [13]:
  - Characterized by predominantly eosinophilic infiltrates in the myocardium leading to endocardial fibrosis with thrombus formation, valve fibrosis, biventricular failure, and arrhythmias, generally evolving over many weeks.
  - May occur in association with systemic diseases such as hypereosinophilic syndromes or eosinophilic granulomatosis with polyangiitis; drugs or toxins such as Clozapine and sulfonamides; Löffler's endomyocardial fibrosis; or parasitic diseases such as *Toxocara canis*. An etiology is identified in about 2/3 cases.
  - High-dose corticosteroids may be beneficial for systemic disease. Surgical treatment has been used in endomyocardial fibrosis.
  - Idiopathic acute necrotizing eosinophilic myocarditis (ANEM): presents in fulminant fashion, with sudden cardiac death or rapidly progressive HF, and may be accompanied by peripheral eosinophilia, and rash and fever. It is often a type of hypersensitivity myocarditis with eosinophilic (and lymphocytic and histiocytic) infiltration but less necrosis, and often due to a new medication (e.g., penicillins, sulfa drugs, isoniazid, thiadizes, dobutamine).
- Lyme myocarditis
  - Can occur in association with infection by *Borrelia burgdorferi* in patients with history of travel to endemic areas, tick bite exposure.
  - Clinical presentation includes AV conduction abnormalities, including transient or permanent complete heart block.
  - Diagnosis of Lyme disease is confirmed by serologic testing
  - Treatment includes treatment of underlying infection with appropriate antibiotics such as ceftriaxone, doxycycline, supportive care of LV dysfunction, permanent pacemaker for development of complete heart block.
- Chagas myocarditis
  - Infection by *Trypanosoma cruzi*, endemic in areas of rural South or Central America.
  - Can present with acute myocarditis or chronic cardiomyopathy.
  - Symptoms include arrhythmia or heart block in 10–20% of infected patients.
  - Diagnosis is suspected in persons from endemic areas and confirmed by serologic testing.
  - No specific treatment but antiparasitic treatment against *T. cruzi* may eradicate disease in acute or sub-acute infection. Supportive care and management of LV dysfunction and arrhythmias.
- Human Immunodeficiency Virus (HIV) myocarditis
  - Prevalence of myocarditis in HIV-infected patients as high as 70% in autopsy series.
  - Characterized by non-specific myocardial infiltrates with LV dysfunction, although pathogenesis is unclear. Could be related to HIV infection itself, direct myocardial co-infection or effects from anti-retroviral therapy.
  - Highly Active Anti-Retroviral Therapy (HAART) significantly reduces incidence of HIV-associated myocarditis and dilated cardiomyopathy.
- Checkpoint-inhibitor myocarditis [14, 15]
  - This new class of antibody drugs block the progression of cancer cell growth by attacking programmed death-1 (PD-1) pathway. These drugs are applicable to novel treatments in a number of cancers including melanoma.
  - Fulminant myocarditis occurs in ~1% of patients taking checkpoint-inhibitors, with median onset 34 days after starting therapy, with lymphocyte and macrophage infiltrate in the myocardium.
  - In half of patients, besides myocarditis there is no other immune-related side effect.
  - Serial EKG and biomarker monitoring may be considered at each stage of these chemotherapy regimens.

CLINICAL PRESENTATION AND DIAGNOSIS

- Clinical presentation: signs and symptoms can be protean including non-specific and asymptomatic EKG changes, but there is a wide spectrum ranging to cardiogenic shock or even sudden cardiac death
  - Non-specific symptoms of dyspnea, chest pain, or palpitations are frequent.
    - Chest pain could reflect co-morbid pericarditis (elevations of troponin in the setting of pericarditis may reflect epicardial myocyte inflammation, and sometimes be called "myopericarditis").
  - The LV may become dilated and dysfunctional or remain non-dilated and exhibit a restrictive phenotype, depending on the type of myocarditis.
  - The cardiologist must maintain a high index of suspicion to diagnose a myocarditis.
  - Patients may report viral prodrome with fevers, myalgias, respiratory or gastrointestinal symptoms.
- Examination: no findings are specific for myocarditis, as findings may reflect signs of heart failure.
- Diagnosis of acute myocarditis remains largely clinical, although there is an increasing use of non-invasive imaging techniques.
  - EKG
    - All patients with suspected myocarditis should have an EKG performed.
    - EKG may show ST segment depressions, non-specific ST-T wave abnormalities, occasionally ST elevations in two or more contiguous leads, which can mimic an ST-elevation myocardial infarction (STEMI) (but in myocarditis, usually concave morphology and without reciprocal changes).
    - Atrioventricular (AV) block is more common in giant cell myocarditis, Lyme carditis, or cardiac sarcoidosis, and rare in lymphocytic myocarditis.
    - Ventricular tachycardia (VT) is more common in giant cell myocarditis or cardiac sarcoidosis.
  - Biomarkers
    - Cardiac enzyme elevations occur in a minority of patients, troponin has more specificity (89%) than CK-MB subunits but overall limited sensitivity (34%) in the diagnosis of myocarditis [16]. Data on high sensitivity troponin should be forthcoming. However, elevations in troponins or natriuretic peptides are not specific, and normal values cannot exclude myocarditis.
    - Inflammatory markers (ESR and CRP) are non-specific.
    - Viral serologies are of low yield and not routinely recommended in diagnosing acute viral myocarditis, as there is a high population prevalence of IgG antibodies to "cardiotropic" viruses (see Table 27-2) [5].
    - Auto-antibodies are being investigated as predictive factors (e.g., anti-heart antibodies, anti-sarcolemma antibodies).
  - Non-invasive Imaging
    - Echocardiogram findings vary, and are non-specific for myocarditis, but all patients with suspected myocarditis should undergo an echocardiogram, which is also useful for excluding other known causes of acute HF and cardiomyopathy [17].
      - Left ventricular (LV) dysfunction is frequently observed.
      - LV dilatation may or may not be present. The LV may be non-dilated in fulminant myocarditis, and the ventricular walls may be thickened.
      - Segmental wall motion abnormalities can mimic myocardial infarction (MI).
    - Nuclear imaging is not routinely used in diagnosing myocarditis.

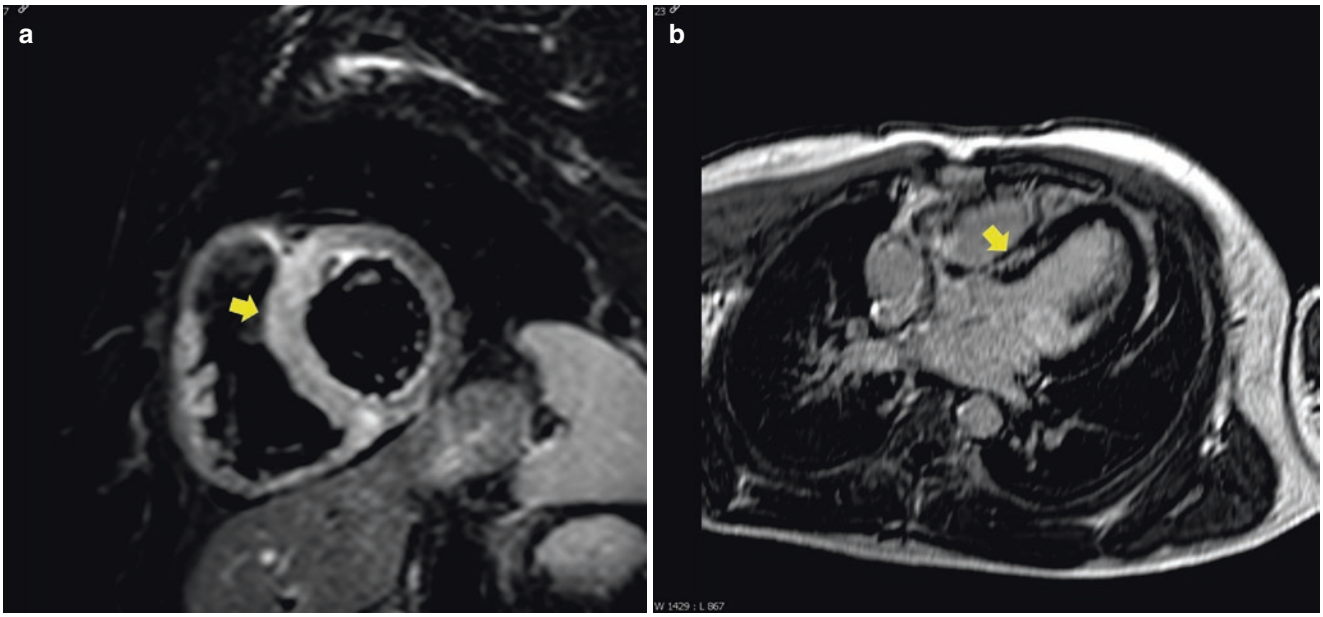

FIGURE 27-2

CMR findings in myocarditis. (**a**) T2-weighted CMR image with focal high signal intensity of septum (arrow), which is consistent with regional edema. In the absence of late gadolinium enhancement (LGE), edema suggests reversible myocardial injury. (**b**) Myocardial LGE in the septum (arrow) of a different patient, which indicates presence of fibrosis. Focal LGE typically is localized to the subepicardial regions in myocarditis, but may be multi-focal or diffuse in distribution

  - However, fluorodeoxyglucose positron emission tomography may be useful for evaluating for cardiac sarcoidosis.

- Cardiac MRI (CMR) is becoming a routine non-invasive test for the diagnosis of acute myocarditis [18], especially in stable patients, though it should not displace endomyocardial biopsy when indicated in certain acute presentations (see below).
- Per Lake Louise Criteria, CMR findings are consistent with myocarditis if 2 of 3 of the below parameters are positive/pathologic [19] (Fig. 27-2):
  - T2-weighted images, for assessment of myocardial edema
  - T1-weighted sequences, pre- and post-contrast, for detection of myocardial hyperemia
  - Late gadolinium enhancement (LGE), for detection of myocardial necrosis/fibrosis
    - The LGE pattern in myocarditis is more typically subepicardial and mid-myocardial, sparing the endocardium (conversely, endocardial predominant LGE more likely reflects ischemic cardiomyopathy).
- CMR with Lake Louise criteria has a positive predictive value 91% and a diagnostic accuracy of 78% in the diagnosis of acute myocarditis [19].
  - Using a strategy of CMR or endomyocardial biopsy should be able to diagnose myocarditis in 95% of cases of chest pain without coronary artery disease [20].
- CMR tissue characterization also confers prognostic information, with presence of LGE conferring double risk of major adverse cardiovascular events. Septal and mid-wall LGE, or a patchy distribution of LGE, were most correlated with major adverse cardiovascular events [21].

- Histopathology
  - Endomyocardial biopsy is part of gold standard of diagnosis with histopathologic classification according to the Dallas Criteria.
  - Endomyocardial biopsy can identify the type of inflammatory infiltrate and give information on the underlying etiology (see Tables 27-1 and 27-2), and this information can be useful for excluding infection so that immunosuppressive medications can be started, and planning treatment options.
  - Nevertheless, endomyocardial biopsy is not done routinely in practice because of imitations, including: significant sampling error on endomyocardial biopsy due to patchy nature of myocarditic inflammation, intra-observer variability, and risks of cardiac perforation and death with native heart biopsy.
    - Sensitivity of endomyocardial biopsy using Dallas Criteria for the diagnosis of suspected myocarditis is estimated to be about 10% [22].
      - There is concern that endomyocardial biopsy studies may underestimate prevalence of myocarditis.
    - Diagnostic yield of endomyocardial biopsies might be improved by
      - Immunohistological evaluation to enable specific microbiologic detection and quantification of infiltrates
      - Molecular analysis with DNA-RNA extraction and amplification of the viral genome with polymerase chain reaction (PCR)
      - MRI-guidance, where available
      - Biopsy earlier in the disease course
  - Listed indications for endomyocardial biopsy are derived from a 2007 ACC/AHA Guideline [23], and specify 14 different scenarios and the recommendation grade.
    - There are only two class I scenarios, generally acute deterioration of unknown etiology not responding to conventional therapies:
      - Unexplained, new-onset HF of <2 weeks duration with associated hemodynamic insult (LV may be normal-sized or dilated)
      - Dilated ventricle with 2 weeks to 3 months of symptoms, new ventricular arrhythmias or heart block, who fail to respond to usual care within 1–2 weeks
      - These are because myocarditis can progress rapidly, and endomyocardial biopsy is needed to guide the diagnostic and treatment strategy.
    - 11 other scenarios carry class II recommendations, and include suspected allergic reactions, anthracycline cardiomyopathy, unexplained restrictive cardiomyopathy, etc.
    - Unexplained atrial fibrillation is the only class III recommendation.

TREATMENT

- In general, treatment of viral myocarditis is largely supportive, based on conventional HF management following current ACC/AHA guidelines for the management of left ventricular dysfunction except in specific subtypes of myocarditis as discussed below.
- Conventional HF treatment:
  - Angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB)
  - Beta blockers
  - Aldosterone antagonists
  - Diuretics

- Immunomodulatory treatments: Immunosuppressive medications can be trialed after excluding active infection (endomyocardial biopsy ± microbiologic studies like PCR), however routine use is controversial and therapy should be dictated by underlying etiology.
  - Viral/lymphocytic myocarditis: immunosuppression or intravenous immune globulin are not routinely recommended [2].
    - In the Myocarditis Treatment Trial, 111 patients with biopsy proven myocarditis and LVEF < 45% were randomized to conventional HF treatment plus placebo or active immunosuppression (prednisone or cyclosporine). After 24 weeks, there was no significant difference in LVEF, death, or need for cardiac transplantation between the treated versus untreated patients [6].
  - Giant cell myocarditis: combined treatment with immunosuppressants (corticosteroids plus calcineurin inhibitors ± Muromonab-CD3) can improve survival to 91% from less than 10% [24].
    - Other agents that may be considered include azathioprine, antithymocyte globulin, mycophenolate mofetil, or methotrexate, and these are generally used in combination [25].
  - Cardiac sarcoidosis: specific treatment with steroids is also warranted.
  - Eosinophilic cardiomyopathy: high dose corticosteroids may be helpful with systemic disease.
  - Checkpoint-inhibitor myocarditis: high dose corticosteroids are generally used along with cessation of the checkpoint-inhibitor.
  - There is generally no role for non-steroidal anti-inflammatory drugs (NSAIDs).
- Antiviral therapy: there is little role for antiviral treatment in acute myocarditis; however in chronic myocarditis/dilated cardiomyopathy, the BICC (Bioferon in Chronic Viral Cardiomyopathy) trial suggests that treatment with interferon in patients with endomyocardial biopsy-proven enteroviral or adenoviral persistence can lead to elimination of viral genomes and improvement in LV function [26].
- Mechanical circulatory support: intra-aortic balloon pump (IABP), LV assist devices (LVAD) or extracorporeal membrane oxygenation (ECMO) may be useful in fulminant and acute myocarditis as bridge to spontaneous recovery or transplantation, in patients with persistent shock unresponsive to medical therapy.

FOLLOW-UP

- Clinical follow-up after acute myocarditis
  - There is a need for close follow-up after acute myocarditis, given the increased incidence of evolution to chronic dilated cardiomyopathy.
  - Recommendations are for follow-up at 1–3 month intervals with reassessment of cardiac function at 1 month, 6 months and then yearly.
  - Athletes with definite or presumed diagnosis of myocarditis should refrain from competitive sports for 3–6 months afterward due to risk of arrhythmia, with resumption of intensive physical activity only after normalization of LV function, biomarkers of myocardial injury and inflammation have normalized, and in the absence of significant arrhythmia on EKG/Holter/exercise EKG [27].

ACC/AHA GUIDELINES SUMMARY

- There are no specific ACC/AHA guidelines with regards to management of myocarditis. However, recent AHA scientific statement on fulminant myocarditis [28] and guildelines for the management of LV dysfunction, use of endomyocardial biopsies, and arrhythmias apply in their appropriate context.

QUICK REVIEW

- Myocarditis often occurs in the setting of infection of the myocardium by microbiologic agents (most commonly viruses), and resulting autoimmunity leading to damage of cardiac myocytes and LV dysfunction.
- The presenting symptoms and signs of myocarditis may be protean and heterogenous, ranging from asymptomatic EKG changes to severe dysrhythmias and cardiogenic shock; some may mimic acute MI. The cardiologist must maintain a high index of suspicion for myocarditis.
- Diagnosis is largely clinical and can be made through non-invasive testing such as CMR. Endomyocardial biopsy is only indicated in a select percentage of patients who do not respond to conventional HF treatment.
- Treatment of myocarditis remains largely supportive; mostly guideline-based management of LV dysfunction and may include use of LVAD and other mechanical circulatory support when indicated (e.g., fulminant myocarditis, giant cell myocarditis).
- Prognosis depends on the underlying etiology of myocarditis. Fulminant myocarditis classically is believed to have highest chance of spontaneous complete resolution.
- There is no role for immunosuppression in acute lymphocytic myocarditis, although in specific etiologies such as giant cell myocarditis, immunosuppressive therapy can improve survival.
- There is a high rate of spontaneous recovery of cardiac function in acute myocarditis, although 10–20% of patients can progress to a chronic dilated cardiomyopathy.

REVIEW QUESTION [12]

A 53-year-old man without prior personal or family medical history was admitted to your cardiac intensive care unit with hypotension to 88/53 mmHg and recurrent monomorphic ventricular tachycardias hours after he had defibrillator placement, 4 weeks after suffering an out-of-hospital cardiac arrest and being found to be in monomorphic ventricular tachycardia with rates exceeding 200 bpm. Results of the evaluation from two prior hospitals and outpatient cardiology clinic visits were notable for:

- angiography without evidence of obstructive coronary artery disease;
- transthoracic echocardiography with moderate LV systolic dysfunction worst in inferior and septal territories, and LV dilatation;
- CMR with biventricular dysfunction, myocardial edema, an elevated T2 signal ratio of myocardium:skeletal muscle of 2.4 (normal $\leq$ 1.9), and patchy nodular foci of LGE in the subepicardium of septum and inferolateral walls with some mid-wall and subendocardial extension;
- EKG showing evolution of a new first-degree AV block, new right bundle branch block, and new left anterior hemiblock.

On admission, repeat transthoracic echocardiography shows severe LV and mild right ventricular hypokinesis, LV dilatation, and thinning of the interventricular septum, and laboratory studies were normal except for mild increases in NT-pro B type natriuretic peptide at 3942 pg/mL (normal 0–900) and troponin T at 1.10 ng/mL (normal < 0.03). Overnight, ventricular tachycardias persist, despite trials of amiodarone, lidocaine, and esmolol and the blood pressure remains marginal.

Which of the following is the next best diagnostic step?

a) Epinephrine administration for hypotension
b) CMR
c) Empiric combination immunosuppression
d) Endomyocardial biopsy and initiation of combination immunosuppression
e) Repeat coronary angiography with fractional flow reserve

Answer

(d) Endomyocardial biopsy and initiation of combination immunosuppression

Cardiologists must maintain a high index of suspicion for giant cell myocarditis, which can have a fulminant presentation with shock and arrhythmias, and often require mechanical circulatory support. In this case, the rapidly progressing cardiac disease, in the absence of prior history or prodrome, characterized by recurrent ventricular tachyarrhythmias and evolution of multi-location conduction disease (with new first-degree AV block and bifascicular block), should raise concern for giant cell myocarditis. In fact this is one of the two class I ACC/AHA recommendations for endomyocardial biopsy: new-onset HF (2 weeks to 3 months duration) with a dilated LV, and either new ventricular arrhythmias, second or third degree AV block, or failure to respond to optimal HF care within 1–2 weeks. Giant cell myocarditis often presents in the fourth or fifth decade of life, and presentations

include HF or new cardiomyopathy in ~75%, ventricular tachydysrhythmia in ~15%, and heart blocks in ~5%. Beta agonists can often worsen the underlying ventricular arrhythmias, and thus early mechanical circulatory support strategies may be necessary in these patients. While elements of the presentation could be ischemic, the coronary angiogram was also non-obstructive 4 weeks ago. While CMR would be insightful to detect acute inflammation, this would only indicate presence of myocarditis, and may not specifically indicate giant cell myocarditis. Making this distinction is critical, since the prognoses is worse in giant cell myocarditis, and treatment strategy in myocarditis in general is dependent on the underlying etiology. In this patient, biopsy showed a multicellular inflammatory infiltrate with primarily macrophages and lymphocytes, along with giant cells. Multi-drug immunosuppression was initiated but the patient required mechanical circulatory support for persistent cardiogenic shock and ventricular tachycardia, and ultimately a heart transplant.

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CHAPTER 28

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Cardio-Oncology and Tumors of the Heart

CHAPTER OUTLINE

ABBREVIATIONS

5-FU	5-fluoro-uracil
ACEi	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ARNI	Angiotension receptor neprilysin inhibitor
AVB	Atrio-ventricular block
CAD	Coronary artery disease
CMP	Cardiomyopathy
DOAC	Direct oral anticoagulant
EMB	Endomyocardial biopsy
ESR	Erythrocyte sedimentation rate
FFR/iFR	Fractional flow reserve/instantaneous wave-free ratio
GDMT	Goal directed medical therapy
GLS	Global longitudinal strain
IAS	Interatrial septum
ICI	Immune checkpoint inhibitor
IL-6	Interleukin 6
IMRT	Intensity-modulated radiation therapy
LQTS	Long QT syndrome
MCRA	Mineralocorticoid receptor antagonist
MTX	methotrexate
MUGA	Multigated acquisition
PAD	Peripheral arterial disease
PR	Pulmonic regurgitation
PS	Pulmonic stenosis
RFs	Risk factors
ROS	Reactive oxygen species
SCD	Sudden cardiac death
TKI	Tyrosine kinase inhibitor
TR	Tricuspid regurgitation
TS	Tricuspid stenosis
VEGFi	Vascular Endothelial Growth Factor inhibitors
VT	Ventricular tachycardia
VTE	Venous thromboembolism
XRT	Radiation therapy

SECTION I: CARDIO-ONCOLOGY

Introduction

The delineation of the biology of cancer in the twentieth century led to exponential growth in the cancer treatment, leading to improved patient survival. Recently, novel therapeutic agents targeting the host's immune system, protein products of genetic recombination, and the tumor microenvironment were developed. While oncology drug development has led to marked improvements in remission rates and patient survival, it has also led to better understanding of cardiovascular consequences of this armamentarium of therapeutics. Many patients undergoing cancer treatment experience adverse cardiovascular complications due to oncologic therapy superimposed on preceding cardiac disease or cardiovascular risk factors, making cardiovascular events the second most common cause for morbidity and mortality in cancer survivors. Management requires the expertise of a cardiologist in conjunction with the patient's treating oncologist, which has led to the creation of cancer survivorship programs dedicated to longitudinal follow-up and integrated management of cancer survivors by cardiologists, oncologists, and nephrologists.

GENERAL RISK FACTORS, PREVENTIVE, SURVEILLANCE, AND MONITORING STRATEGIES FOR CARDIOTOXIC THERAPIES

Risk factors:

- High-dose anthracyclines (doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2)
- RT ≥30 Gy with heart in treatment field
- Lower anthracycline doses doxorubicin ≤250 mg/m^2 or epirubicin ≤600 mg/m^2 with RT <30 Gy and heart in treatment field
- Lower-dose anthracyclines or trastuzumab alone and presence of RFs:
  - ≥2 of following: smoking, HTN, diabetes, dyslipidemia, obesity
  - Age ≥60 at diagnosis/treatment
  - Compromised cardiac function: low-normal EF (50–55%), prior MI, ≥moderate valvular disease
- Lower-dose anthracyclines followed by trastuzumab (sequential therapy)
- Controversial risk assessment for lower-dose anthracyclines or trastuzumab alone without additional RFs, lower-dose RT (<30 Gy) with heart in treatment field and no additional RFs or cardiotoxic exposures, kinase inhibitors [1]

Preventative strategies prior to chemotherapy

- Avoid cardiotoxic therapies if alternatives exist without compromising cancer-specific outcomes
- Assess/optimize CV RFs
- ✓ TTE prior to cardiotoxic therapies [1]

Preventative strategies during chemotherapy

- Screen for and manage CV RFs
- Consider dexrazoxane (limited approval in adults), continuous infusion or liposomal doxorubicin if high-dose anthracycline therapies are planned
- Minimize RT if mediastinal RT is required and attempt to exclude the heart as much as possible (i.e. breath holding, IMRT, proton therapy) [1]

Preferred surveillance and monitoring during treatment

- Complete H&P in those with potentially cardiotoxic therapies
- If symptoms/signs are concerning for cardiotoxicity, testing may include:
  - TTE (3D LVEF, 2D Simpson's EF, consider GLS)
  - cMRI
  - MUGA
  - Cardiac biomarkers (Tn, BNP or NT-proBNP)
- No strict recommendations on continuation of chemotherapy if cardiac dysfunction is identified (discussion between cardiologist, oncologist is needed)
- Suggest routine TTE in patients with metastatic breast cancer continuing on trastuzumab indefinitely (but no guidelines on frequency)
- Most cardiotoxic chemotherapy patients should undergo routine post-chemo LV function assessment (depends on cardiac RF's, use of RT and dose of anthracyclines).
- Biomarker use (i.e. troponin, BNP) is not routine and case-dependent [1]

Preferred surveillance and monitoring after treatment

- Complete H&P in cancer survivors with prior cardiotoxic therapeutics
- TTE 6–12 months after completion of cancer-directed therapy in asymptomatic patients at increased risk of cardiotoxicity (or cMRI if TTE limited)
- No recommendations on frequency and duration of surveillance in those at increased risk who are asymptomatic after their 6–12 month follow up post-treatment TTE
- Long-term management of CV RFs as part of long-term follow-up care [1]

ANTHRACYCLINES AND CARDIOTOXICITY

- Agents: doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone
- Mechanism: inhibit topoisomerase IIb/RyR/SERCA in cardiomyocytes, activate apoptosis, altered Ca^{2+} homeostasis, increased ROS, mitochondrial iron overload, decreased autophagy
- RFs: cumulative dose (at doxorubicin 400 mg/m^2, 5% develop HF, then exponentially increases), age (>60 or <4 years old), female, pre-existing CAD/HF or CV RFs, mediastinal RT, combination with other cardiotoxic agents (i.e. trastuzumab)
- Complications: LV dysfunction dilated CMP, SCD, arrhythmias (SVT/VT/AVB), myopericarditis (mitoxantrone)
- Incidence
  - 9% overall; median time 5–9 months
  - Hyperacute/acute (during therapy—CMP improves with cessation), subacute (<1 year—usually develop significant cardiac dysfunction), or chronic (1–30 years); 98% occur in first year
- Diagnosis: definitive by EMB (cytosolic vacuolation, lysis of myofibrils, cellular swelling); otherwise—diagnosis of exclusion
- Monitoring: pre-chemo TTE (alternatively, MUGA or cMRI), TTE at 6 months
- Prevention:
  - Dose-reduction, continuous infusion (over 48–96 h) rather than bolus infusion (reduces peak levels)
  - Liposomal or PEGylated doxorubicin
  - Dexrazoxane (an intracellular iron chelator thought to block ROS, inhibit topo-IIb)—used if >300 mg/m^2 doxorubicin AND metastatic breast cancer

  - Limit taxane co-administration (reduces doxorubicin clearance)
  - Limit cumulative doses to daunorubicin <800 mg/m^2, doxorubicin <360 mg/m^2, epirubicin <720 mg/m^2, mitoxantrone <160 mg/m^2, idarubicin <150 mg/m^2

- Treatment:
  - Treat clinical HFrEF with GDMT (i.e. ACEi/ARB/ARNI, beta-blocker, MCRA, ICD, CRT per ACC/AHA guidelines)
  - Exercise can limit doxorubicin-induced LV dysfunction
- Discontinuation criteria (for anthracycline):
  - Asymptomatic + LVEF decline >10% AND LVEF <40%
  - Symptomatic HF + LVEF decline
  - Asymptomatic decline to 40–50%
  - >15% reduction to LVEF <50%
  - Recommend against re-challenge if CMP occurs unless palliative/curative intent
- Prognosis with treatment:
  - 11% recover EF
  - 71% improve >5% of LVEF
  - 18% no EF recovery (10% 5-year cardiac death) [1]

TRASTUZUMAB (ANTI-ERBB2/HER2 ANTIBODY)

- Mechanism: unclear; *erbB2 −/−* mice develop dilated CMP, structural/functional changes in contractile proteins and mitochondria
- RFs: age, CV RFs, diabetes, prior anthracyclines, paclitaxel, cyclophosphamide, lower baseline EF
- Complications: non-dose-dependent, usually reversible CMP
- Incidence: 6.2% HFrEF at 1-year, 20.1% at 5-years (13.5% of patients require treatment interruption, 30% of which are due to CHF (70% are asymptomatic LVEF decline))
- Diagnosis:
  - If LVEF declines >15% from baseline **OR**
  - LVEF declines >10% from baseline **AND** EF<50%
  - Monitor with LVEF prior to and every 3 months while treating with trastuzumab
- Treatment:
  - Interrupt therapy for 4 weeks
  - Start ACEi/GDMT, can reinitiate HER2i therapy if EF recovers
  - Permanently discontinue HER2i if LVEF reduction occurs three times
- Prognosis: if LVEF decrements, 85% of those re-challenged on GDMT will have a stable LVEF
- Alternative HER-2 inhibitors: pertuzumab, T-DM1 (a trastuzumab conjugated to cytolytic emtansine with less cardiotoxicity)—both with similar survival to trastuzumab; lapatinib (an intracellular antagonist) has 2–5% cardiotoxicity at 4.5 year follow-up, 2–3% with CHF but worse survival; neratinib (no cardiotoxicity) but only evaluated for early stage breast cancer (not metastatic) [1]

FLUOROPYRIMIDINES (5-FU AND ITS PRODRUG, CAPECITABINE)

- Mechanism: endothelial injury, vasospasm, coronary artery thrombosis, autoimmune arteritis
- RFs: CAD, CMP, CKD, prior symptoms, longer infusions, leucovorin absence, first cycle

- Incidence: 1.2–18% manifest with MI (usually STEMI), 7–10% silent MI, similar incidence between 5-FU and capecitabine; also associated with stress-induced CMP [2]
- Timing: during first/second infusion (~3 to 18 h after initiation, ends shortly after conclusion)
- Diagnosis: EKG
- Treatment:
  - Nitrates, diltiazem, or verapamil
  - Bolus dosing (shorter infusions daily for 5 days) rather than 24-h infusion [3]
  - Hold chemo 2–4 weeks, start GDMT, await EF recovery
- Prognosis: re-challenge requires consent for possible diffuse coronary vasospasm, death (82–100% recurrence rate); recommend pretreatment with diltiazem verapamil, or nitrates, and monitoring with telemetry and in-hospital infusion

RADIATION-INDUCED HEART DISEASE

- Mechanism: dose-dependent, atheromatous plaques, neointimal hyperplasia, ROS-mediated fibrosis, neuropathy [3–7]
- Risk factors: >40 Gy OR >30 Gy + anthracycline exposure, <50 years, >2 Gy/day fractions, anterior-/left-sided XRT, proximity to heart, absent shielding, CV risk factors, pre-existing CAD
- Complications: CAD (Left main, LCx, RCA most exposure during Hodgkin's treatment [4], often XRT results in ostial LM, ostial LAD lesions; prox-/mid-LAD lesions in breast cancer); CVA; stenotic/regurgitant valvular disease; restrictive interstitial myocardial fibrosis (~3% at 10 years); pericardial constriction (the most common clinical event in up to 7% of Hodgkin's survivors), 19.1-fold increased rate of PPM placement after chest XRT; conduction abnormalities (from incomplete RBBB to AVB); PPM malfunction if neutron-producing XRT; autonomic dysfunction (higher resting HR, abnormal HR/BP response to exercise) due to vagal nerve involvement (i.e. mantle XRT) [4, 8]
- Incidence:
  - XRT carries a 2.2- to 12.7-fold increased cerebrovascular risk in breast and Hodgkin's survivors, 6–7% at 25 years after head and neck XRT [6]
  - CAD risk four- to seven-fold increased, usually occurs 12 years after XRT (25% risk of ischemia/SCD at 25 years)
  - Valvular disease in 10% (~20 years after XRT exposure) with aortic root/cusp and mitral annular or basal/mid-leaflet calcification (spares tips/commissures)
  - Aortic stenosis requiring surgery is increased ninefold, median of 22 years
  - ASE/EACVI recommend screening TTE at 10 years post-XRT and serially every 5 years thereafter
- Timing: 10–20 years s/p XRT, cumulative incidence up to 50% at 40 years
- Diagnosis: screen for CAD at 10–15 years (due to inflexion point ~8 to 10 years) after initial cancer treatment and continue lifelong [5]; if mediastinal XRT, screen every 5 years at 5 years post-treatment (given atypical/silent presentations)
- Prevention: limit XRT exposure with proton therapy, respiratory gating, multiple or rotational sources of XRT, IMRT
- Prognosis: possibly worse PCI outcomes after XRT [9]; worse surgical outcomes due to LIMA/RIMA in XRT field, XRT-fibrosis and calcification [10]

IMMUNE CHECKPOINT INHIBITORS (ICIS):

- Mechanism: CTLA4 (inhibitor: ipilimumab) suppresses peripheral T-cells; PD-1 (inhibitors: pembrolizumab, nivolumab) and PD-L1 (inhibitors: avelumab, atezolizumab, durvalumab) dampen T-cell response (i.e. melanoma and lung cancer have higher tumor expression of PD-L1)

- Complications:
  - Ipilimumab causes autoimmune myopericarditis (0.27% risk of myocarditis if combined with nivolumab)
  - Pembrolizumab causes autoimmune myocarditis, sinus tachycardia, AF, SCD likely 2/2 autoimmune process
  - Nivolumab causes AV block, rare cases of ventricular arrhythmias, possibly from myocarditis (0.06% risk of myocarditis if nivolumab used alone)
- RFs: autoimmune disease, diabetes
- Incidence:
  - Monotherapy carries 0.06–1% risk of ICI-myocarditis
  - 0.5% risk with PD1 inhibitors
  - 2.4% with PD-L1 inhibitors
  - 3.3% with CTLA4 inhibitors
  - 2.4% when PD1 and CTLA4 inhibitors are combined [11]
- Diagnosis: nonspecific and mild with fatigue, CP, myalgias, SOB, syncope, OR severe with SCD, tachy-/bradyarrhythmias, fulminant myocarditis, decompensated CHF or cardiogenic shock—need a high index of suspicion: but must consider alternate etiologies in the differential diagnosis
  - 75% abnormal EKG (ST, QRS/QT prolongation, conduction abnormalities, diffuse T wave inversions, Q waves, ventricular arrhythmias, local/diffuse ST elevation)
  - 90% with TnT elevation
  - 60% with elevated NT-proBNP
- Timing: median presentation ~1 month (delay in amplification of T cell response by ICI); most within 3 months
- Diagnosis: ✓ troponin, BNP, TTE, consider cMRI or EMB depending on stability or severity of presentation
- Monitoring:
  - ASCO recommendations suggest baseline ECG and troponin (especially if dual therapy)
  - If cardiac symptoms arise: ✓ EKG, TnT, TTE, consider cMRI, stress/cath/EMB
- Treatment of ICI myocarditis:
  - CV symptoms: hold ICI
  - Suspected/confirmed: methylprednisolone 1 g/day for 3 days, then 1 mg/kg daily for 1–3 months
  - Augment with steroid-sparing agents if able (i.e. mycophenolate mofetil, infliximab—if no HF, or tacrolimus)
  - Cardiogenic shock/unstable: consider anti-thymocyte globulin, IVIg, plasma exchange [11, 12]
- Discontinuation criteria:
  - Permanently stop if abnormal cardiac testing persists
  - If recovery occurs with immunosuppression and it is weaned off, monitor off of immunosuppression and consider monotherapy with ICI with serial cardiotoxicity monitoring going forward (high risk of recurrence) [11]

ACS IN CANCER

- Mechanism: thrombocytopenia not protective and is associated with increased thrombogenicity; increased risk of stent thrombosis in those with cancer; patients on chemotherapy have delayed stent re-endothelization
- Diagnosis: coronary angiography ± PCI guided by IVUS/FFR/iFR/OCT
- Treatment:
  - Heparinization if platelets <50,000: utilize doses of 30–50 U/kg for initial dosing
  - Aspirin can be given safely when platelets >10,000 in active ACS
  - P2Y12i reserved for platelets >30,000 (clopidogrel when platelets 30,000–50,000, ticagrelor/prasugrel when >50,000)
  - Avoid GP IIb/IIIa inhibitors when platelets <50,000 [13, 14]
- Vascular access considerations (i.e. consider femoral access after breast XRT/mastectomy)
- CABG reserved for platelets >50,000 in an otherwise reasonable candidate
- Prognosis: newer generation drug-eluting stents may permit DAPT cessation after as early as 1 month (general DAPT guidelines should still be applied per ACC/AHA guidelines) [13, 14]

ATRIAL FIBRILLATION

- RFs: lung resection (12.6%); **ibrutinib** (metabolized by CYP3A4: three to fourfold increased risk of AF, ~11%, also associated with increased risk of clotting and bleeding, making anticoagulation difficult); see Table 28-1 for specific chemotherapeutics [15, 16]
- Incidence: risk is doubled in cancer patients (~2% at baseline, ~4% after diagnosis)
- Treatment:
  - CHA_2DS_2-VASc and HAS-BLED not validated in cancer
  - Prefer LMWH given risk of variable INR with warfarin
  - Meta-analyses of patients with cancer in DOAC trials suggests they are safe (caution with CYP3A4-dependent chemotherapeutic metabolism
  - Caution with diltiazem, verapamil, or amiodarone for ibrutinib-related AF due to concomitant CYP3A4 metabolism (should use beta-blockers)
  - No data supporting ablation [15–18]

THROMBOEMBOLIC DISEASE/PAD/VTE

- RFs:
  - 1) Host: older age, female, African ethnicity, infection, CKD, pulmonary disease, obesity, thrombophilia, performance status, surgery, hospitalization, indwelling catheters, Raynaud's
  - 2) Cancer: metastatic pancreatic, breast, colorectal, lung cancers (esp. adenocarcinomas)
  - 3) Drugs: anthracyclines, taxanes, platinum-based chemo, VEGFi, hormonal therapies, aromatase inhibitors; arterial toxicity increases with L-asparaginase, platins, methotrexate, 5-FU, paclitaxel

- Incidence: 1% overall, twofold increase risk of stroke after mediastinal/cervical/cranial XRT with increased carotid atherosclerosis >10 years after XRT
- Monitoring: Carotid Duplex 5 years after XRT for head and neck cancer, lymphoma
- Treatment: edoxaban safe in cancer (believed to be a DOAC class effect); choose DOAC based on pharmacokinetics, CYP metabolism and site of cancer [19, 20]

QTC PROLONGATION

- RFs: advanced age, female, heart disease, CKD, MI, impaired hepatic drug metabolism
- ✓ CYP450 interactions with chemotherapeutic agents (especially anti-emetics)
- Screen for electrolyte disturbances, hypothyroidism, LQTS, history of syncope [20]

PERICARDITIS

- RFs: cyclophosphamide, cytarabine, bleomycin, pericardial/mediastinal tumors, XRT (in 2–5%, 2–145 months post-XRT) (Table 28-1)

TABLE 28-1

SPECIFIC CHEMOTHERAPEUTICS AND THEIR CARDIOTOXICITIES

DRUG	COMPLICATIONS	DRUG	COMPLICATIONS
Antimetabolites		**Alkylators**	
Pentostatin	Ischemia CHF	Busulfan	Endocardial fibrosis (case reports only)
Cytarabine	Steroid-responsive pericarditis	Cisplatin	SVT Bradycardia LBBB Vasculotoxic—Raynaud's, HTN, CVA, MI, iCMP Arterial thrombosis (2%) Hypomagnasemia a/w AF, ventricular arrhythmias Volume overload due to large infusional volume
Fludarabine	Hypotension Chest pain Cardiotoxicity if combined w/ melphalan	Cyclophosphamide	Hemorrhagic myopericarditis (a/w high-dose protocols)—usually death within 1 week of treatment, treatable with steroids
Gemcitabine	SVT	Ifosfamide	Myocardial hemorrhage Arrhythmias CHF
Methotrexate	SVT VT Syncope MI		
Microtubule Inhibitors		**Antitumor Antibiotics**	
Vinblastine, vincristine	HTN, MI, vaso-occlusive complications (≤25%)	Bleomycin	Pericarditis CAD/MI
Docetaxel	Conduction abnormalities, syncope, angina/MI (1.7%)	Mitomycin C	CHF (especially if w/ anthracyclines
Eribulin	QTc prolongation		

TABLE 28-1

(CONTINUED)

DRUG	COMPLICATIONS	DRUG	COMPLICATIONS
Paclitaxel	Bradycardia (29%), CHB, CMP which potentiates doxorubicin toxicity), angina/MI (1–5%)		
VEGF inhibitors		**Monoclonals**	
Afilbercept *(VEGFR 1/2 fused to IgG1 Fc)*	HTN Arterial thromboses	Alemtuzumab (CD52)	Arrhythmias CHF
Bevacizumab	HTN *(11–45%, high risk, new or destabilizing existing HTN usually occurring in first cycle, severe in 20%, due to NO inhibition and vascular rarefaction, redox, thrombotic renal microangiopathy and glomerular injury)—beware of concomitant NSAID, EPO, steroid use, consider nebivolol to increase NO, beware CYP3A4 interactors which increase* [VEGFi]*—treat to target <130/80, monitor throughout first cycle, then every 2–3 weeks* Arterial thrombosis (3.8%) LV dysfunction (2%) CHF NYHA III/IV (1%)	Cetuximab (EGFR inhibitor)	CHF SCD (esp if w/XRT, platins, 5-FU)—black box warning for cardiopulmonary arrest and SCD Severe hypomagnasemia
Ramacirumab	HTN Arterial thrombotic events	Erlotinib	VTE (4–10%) Acute MI with multivessel coronary spasm (2.3%)
Sorafenib	HTN (1.7%)	Rituximab (CD20)	Arrhythmias Angina
Sunitinib	HTN (1.4%)		
Topoisomerase inhibitors		**Immunomodulators**	
Amsacrine Etoposide Teniposide	Vasospastic angina QTc prolongation (hERG inhibition)	IFNa	MI Atrial/ventricular arrhythmias
		IL-2	Capillary leak syndrome SVT/AF (9.7–17%) VT (0.4–1.1%)
		Lenalidomide	VTE Arterial thrombosis (including MI, CVA)—<5% if as monotherapy, 10–20% if given with dexamethasone in Rd regimen
		Thalidomide	SND Bradyarrhythmias (26–53%)—resolves in 12–21 days CHB

TABLE 28-1

(CONTINUED)

DRUG	COMPLICATIONS	DRUG	COMPLICATIONS
Differentiation Agents		**Proteasome Inhibitors**	
All trans-retinoic acid (ATRA)	Pericardial effusions ACS Differentiation syndrome (5–29%)	Bortezomib Carfilzomib	CHF (4% with bortezomib, 25% with carfilzomib) ACS Bradycardia CHF (3.8–5%) Cardiac arrest (1.5%)
AsO_3	QTc prolongation to (26–93%) which can be to >500 ms in >40% of patients Increased risk of TdP Reports of transient CHB necessitating TVP		
TKIs *(Overall associated with SVT, AF, arterial thrombosis, CHF, QTc prolongation)*		**HDACs**	
Alectinib	Bradycardia (8%)	Panobinostat Romidepsin Vorinostat	PE (5.4% for vorinostat) QTc prolongation (9–28% of patients by >60 ms or to >500 ms, therefore, carries black box warning for panobinostat) Increased risk of VT/SCD
Axitinib	HTN Arterial thrombosis LV dysfunction		
Brigatinib	Hypotension Bradycardia		
Ceritinib	Bradycardia (caution if baseline HR < 70, interacts with other CYP3A4 metabolized nodal agents) QTc prolongation		
Cobimetinib	CMP		
Crizotinib	Bradycardia QTc prolongation		
Dasatinib	Severe pulmHTN (occurs 8–40 months after exposure, presents similar to PAH, replace with another TKI, may need steroids CHF (4%)		
Ibrutinib	High risk of AF		
Imatinib	CHF		
Lapatinib			
Nilotinib	QTc prolongation > 500 ms (<1%) SCD (<1%)—black box warning		
Sorafenib	ACS (2.9%)—due to multivessel coronary spasm HTN (a marker of effectiveness		
Sunitinib	CHF (NYHA III/IV in 8%)		
Vandetanib	QTc prolongation (second highest incidence after AsO_3)		
Vemurafenib	QTc prolongation (also CYP3A4)		

- Treatment:
  - Beware colchicine-related immunosuppression and NSAID-associated bleeding
  - XRT-related treated with NSAIDs, colchicine [1, 20]

SECTION II: TUMORS OF THE HEART

Introduction

Tumors of the heart, particularly primary cardiac tumors, are one of the least investigated subjects in oncology. As such cardiac tumors and their associated complications rarely gain clinical attention despite their potentially serious sequela. Early recognition and diagnosis of a cardiac tumor by a combination of clinical symptoms and the use of modern imaging tools, could lead to the institution of appropriate management in a timely manner. This in turn may lead to better morbidity and mortality outcomes for these patients.

See *Chap. 29* for images of cardiac tumors.

INCIDENCE

Primary cardiac tumors

- Rare <0.1% prevalence (0.001–0.3%) [21, 22]
- 75% are benign [23–25]

Secondary tumors (metastatic)

- Secondary tumors 20–40 times more common than primary cardiac tumors [26–28]
- Most common: lung, breast, hematological, melanoma
- 9–15% of cancer patients develop cardiac metastasis

CLASSIFICATION [28, 29]

Primary Tumors (Benign or Metastatic)

Tumor can arise from

- Endocardium
- Myocardium
- Pericardium
- Valve tissue
- Cardiac connective tissue

Secondary Tumors (Metastatic)

- Cardiac metastases can arise via:
  - Hematogenous dissemination of cancer cells (i.e. melanoma, lymphoma)
  - Direct extension via adjacent tissues (i.e. lung)
  - Propagation to the RA via SVC and IVC (IVC is classic for renal cancer)
  - Retrograde lymphatic seeding (i.e. breast carcinoma)
- Pericardium most commonly affected (69.4%), followed by epicardium (34.2%) and myocardium (41.8%) then endocardium (5%) [30]
- Paraneoplastic phenomena can also occur such as hypercoagulability, particularly with mucinous neoplasms, can present with non-bacterial endocarditis

TABLE 28-2

INCIDENCE OF CARDIAC METASTASIS

CANCER TYPE	NUMBER OF PATIENTS	% WITH CARDIAC METASTASIS	PREVALENCE (ALL NEOPLASMS) (%)	PREVALENCE (METASTATIC NEOPLASMS) (%)
Mesothelioma	128	48.4	54.2	9.4
Melanoma	79	27.8	34.1	3.3
Adenocarcinoma of lung	460	21	26.1	14.6
Poorly differentiated carcinoma of lung	420	19.5	21.2	12.4
Squamous cell carcinoma of lung	428	18.2	23.4	11.8
Breast carcinoma	427	15.5	20.6	10.0
Ovarian carcinoma	106	10.3	11.6	1.5
Leukemia/lymphoma	711	9.4	17.3	10.1
Stomach carcinoma	360	8	9.8	4.4
Renal cell carcinoma	287	7.3	16.3	3.2

Results are from 622 Cardiac Metastases Out of 7289 Patients with Malignant Neoplasm, Based on 18,751 Autopsies [30]

Common metastatic cancers invading the heart and their prevalence (see Table 28-2: Incidence of cardiac metastasis based on a pathologic series of 7289 autopsies [30]

Melanoma cited as most common metastatic cancer [31]

Carcinoid Syndrome [28]

- Lesions in the right heart chambers, mainly affecting valves (but 15% associated with left-sided valves)
- Fibrous plaque formation results in thickening, shortening and decreased leaflet and cusp motion of tricuspid and/or pulmonic valve (including papillary muscles/cords) and mixed regurgitation and/or stenosis
- A subset present with carcinoid syndrome (flushing, diarrhea, abdominal cramping, wheezing due to serotonin release into circulation); >50% will have associated carcinoid heart disease
- Carcinoid heart disease manifests with right-sided CHF symptoms, more commonly from stenotic right-sided lesions similar to valvular pathology from ergot alkaloid exposure
- Treatment is aimed at underlying process (chemotherapy, usually with somatostatin analogs due to inhibition of vasoactive amines secreted by tumor that drive valvulopathy)

CLINICAL MANIFESTATIONS [29]

Symptoms/signs dependent on **location and size** of tumor and not histopathology.

- Systemic symptoms
  - Resemble vasculitis and connective tissue diseases
  - Fever, weight loss, fatigue, arthralgia, Raynaud's phenomenon
  - Labs—anemia, ↑ WBC, ↑ platelets, ↑ ESR, hypergammaglobulinemia
  - Attributed to secretion of factors like IL-6, endothelin, VEGF

- Cardiovascular symptoms
  - Obstructive (i.e. left atrial tumor like myxoma can present similarly to mitral stenosis)
  - Heart failure
  - Arrhythmias
  - Atypical or non specific chest pain
- Systemic embolization
  - Peripheral thromboembolism
  - Pulmonary embolism
  - Stroke
- Symptoms due to metastasis
  - Pericardial disorders (i.e. tamponade)
  - Pulmonary symptoms
- Majority are clinically silent and only present or discovered at autopsy

Table 28-3: Locations of tumor and likely associated signs/symptoms

TABLE 28-3

LOCATIONS OF TUMOR AND LIKELY ASSOCIATED SIGNS/SYMPTOMS [34, 35]

LOCATION OF TUMOR	SYMPTOMS/SIGNS	MECHANISM FOR UNDERLYING SYMPTOMS/SIGNS
Left atrium	■ Dyspnea ■ Orthopnea ■ PND ■ Pulmonary edema ■ Cough ■ Hemoptysis ■ Edema ■ Fatigue ■ Strokes/TIAs	■ Left heart failure resulting from: 1) Obstruction to circulation i.e. obstruction to atrial or ventricular filling 2) Impairment of mitral valve function (MR) ■ Systemic embolization
Right atrium	■ Fatigue ■ Pulmonary edema ■ Hepatomegaly ■ Ascites ■ Prominent "a" waves in jugular veins	■ Right heart failure resulting from: 1) Obstruction to circulation i.e. obstruction to atrial or ventricular filling 2) Impairment of tricuspid valve function (TS)
L ventricle	■ Arrhythmias ■ Conduction defects ■ Strokes/TIAs	■ Left heart failure resulting from: 1) Obstruction to circulation i.e. obstruction to atrial or ventricular filling 2) Direct invasion of myocardium ■ Systemic embolization ■ Invasion of conduction system
R ventricle	■ Peripheral edema ■ Ascites ■ Hepatomegaly ■ SOB ■ Syncope ■ SCD	■ Right heart failure resulting from: 1) Obstruction to circulation i.e. obstruction to atrial or ventricular filling ■ Pulmonary embolus ■ Invasion of conduction system

DIAGNOSIS

- Often delayed as symptoms mimic more common disorders
- Patients frequently have had multiple investigations as symptoms are not specific
- Usually made based on results of imaging

A) **EKG**: May show atrial enlargement, heart block or arrhythmia
B) **Imaging** (Table 28-4: Imaging used in the diagnosis of cardiac tumors and key features)
C) **Transvenous Biopsy**: not generally warranted if appearance on imaging is typical

TUMOR CHARACTERISTICS AND MANAGEMENT [28, 32]

Basic Principles of Treatment

- Benign tumors—surgical resection but tumor may recur
- Metastatic cancer—dependent on tumor type and origin but prognosis generally poor; surgical therapy rarely results in a true systemic cure but can be considered if hope of a disease-free interval is paramount

TABLE 28-4

IMAGING USED IN THE DIAGNOSIS OF CARDIAC TUMORS AND KEY FEATURES [28, 29, 32]

IMAGING MODALITY	FINDINGS/FEATURES
Chest X-ray	■ Anterior mediastinal mass (teratomas) ■ Calcium deposits (right sided myxomas) ■ Bizarre changes in cardiac silhouette
Tranthoracic echocardiogram (TTE)/Transesophageal echocardiogram (TEE)	■ Noninvasive, readily available ■ High sensitivity (90%) and specificity (95%) ■ Able to depict shape, size, extent and mobility ■ TTE better to visualize ventricular tumors ■ TEE–better visualization and identification of small tumors (<5 mm) [36] ■ Can provide information about any obstruction ■ Contrast helps differentiate between tumor and thrombus
Cardiac CT	■ High resolution allows accurate depiction of tumor morphology ■ Beneficial in defining small lesions therefore useful for staging ■ Can provide some characterization of tumor (X-ray attenuation) but not as accurate as CMR ■ Disadvantages: Use of radioactivity and nephrotoxic contrast medium
Cardiac Magnetic Resonance Imaging (CMR)	■ Non-invasive ■ High resolution ■ Wide imaging range ■ T1 and T2 reflects microenvironment of tumor ■ Used to characterize the composition of the tumor: highly cellular tumors demonstrate restricted diffusion and blood vessel-rich metastases demonstrate avid contrast enhancement
Positron Emission Tomography (PET) Scan	■ Useful in identifying cardiac metastasis, myxomas or lipomatous septal hypertrophy

- Pericardial effusions treated with pericardiocentesis or window
- Extensive myocardial involvement leading to large-scale debridement usually results in poor LV function post-operatively
- Intracavitary lesions leading to decreased cardiac output can be considered for debulking
- These surgeries often require use cardiopulmonary bypass (unless pericardial or epicardial resection is required)

Ongoing Management

- For benign tumors surgery usually curative (95% at 3 years)
- Rhabdomyomas generally spontaneously regress therefore do not require any invasive intervention unless symptomatic
- Malignant primary tumors or metastatic disease
  - Prognosis poor (survival rates < 1 year)
  - Palliative treatment to decrease tumor size
    - Chemotherapy
    - Radiotherapy
    - Surgical resection (poor results and high rates of recurrence)

Table 28-5: Tumor type and their class
Tables 28-6, 28-7, and 28-8: Tumor types, their characteristics and management

TABLE 28-5

TUMOR TYPE AND THEIR CLASS

TUMOR CLASS	TUMOR TYPE
Intracardiac benign primary tumor	Myxomas Lipomas Papillary Fibroelastomas Rhabdomyomas Fibromas Hemangiomas Hamartomas
Intracardiac malignant primary tumors	Sarcomas
EXTRACARDIAC BENIGN PRIMARY tumors	Thymomas Teratomas

TABLE 28-6

INTRACARDIAC BENIGN PRIMARY TUMORS, THEIR CHARACTERISTICS AND MANAGEMENT [29, 32]

INCIDENCE	CHARACTERISTICS	COMPLICATIONS	MANAGEMENT
MYXOMAS			
Most common adult primary tumor Account for approx. 30–50% of primary cardiac tumors Affects 30–60 years age group Found predominantly in women (60–70%) except in Carney complex (more common in men)	75–80% originate from LA (fossa ovalis of interatrial septum with or without a stalk), 20% in the RA, 5% ventricles (free wall) Usually mobile and moves with blood flow Usually in one site but can occur in multiple sites (uncommon) Vary in size (1–15 cm) Usually pedunculated (75%) but can also be sessile or broad based **Carney complex** (7–10% of myxomas)—uncommon familial form; autosomal dominant, *PRKAR1A* gene, associated with cutaneous myxoma, myxoid mammary fibroadenomas, **pigmented skin lesions (lentiginoses)**, **endocrinopathy** (multiple endocrine neoplasia), **unusual nonmyxoma tumors** (testicular tumors, thyroid adenomas/carcinomas, ovarian cysts, psammomatous melanotic schwannoma, breast ductal adenoma and osteochondromyxoma (**consider especially if myxoma is outside of left atrium)** Myxoma versus thrombus: On TTE, myxomas usually are mobile, have demarcated borders, an attachment point, mottled appearance.	Constitutional symptoms (fever, arthralgias, malaise, weight loss, rash thought to be secondary to IL-6 expression) (34%) CHF symptoms (67%)—minority have "tumor plop" on exam Abnormal labs (anemia, elevated ESR) Mimics MS Systemic embolization (stroke/TIA) (29%)	Surgical removal of myxoma and surrounding IAS ± Dacron patch MV annuloplasty, repair or replacement may be required Cardiac auto-transplantation Transplantation Serial TTEs for recurrence (1 year post-op and every 5 years thereafter; annual TTE for Carney Complex patients) [37] Consider genetics referral [38]
LIPOMAS			
Wide range of ages Second most common adult primary tumor (10%) Equal frequency in both sexes	Predominance of fatty cells (adipocytes, usually brown fat, can be mistaken for metastases as they are FDG-avid on PET) [39] Circumscribed, encapsulated tumor Usually located in the subepicardium (LV, RA and IAS) Originate from the endocardium or epicardium Most are sessile or polypoid with large pedunculated base **Lipomatous hypertrophy of the IAS**—noncapsulated hyperplasia and accumulation of adipose tissue in IAS (elderly and obese male)—generally >1.5 cm with 1–8% incidence; thick, bright atrial septum with sparing of fossa ovalis appearing as a "dumb-bell"	CHF due to obstruction to circulation Arrhythmias due to invasion of cardiac conduction system (usually atrial arrhythmias)	Asymptomatic Surgical resection if symptomatic

TABLE 28-6

(CONTINUED)

INCIDENCE	CHARACTERISTICS	COMPLICATIONS	MANAGEMENT
PAPILLARY FIBROELASTOMAS			
Most common tumor of the cardiac valves (75% of valve tumors) and second most common cardiac tumor Affects men and women equally i.e. male 55% Mean age of detection 60 years	Varies in size but generally small (<1 cm) and rarely exceeds 1 cm (range 0.1–1.4) Avascular Pedunculated (45%) Microscopically resembles sea anemones (central core with papillary fronds) 80% found on heart valves and usually on the L side (aortic 36%, mitral 29%, tricuspid 11% pulmonic 7%) 30% asymptomatic characteristic speckled appearance on TTE with stippling near edges CMR with T2 hyperintensity related to connective tissue and mucopolysaccharide matrix Can form nidus for platelet and fibrin aggregation leading to systemic emboli	Dyspnea Cyanosis Embolic events (R- or L- sided) SCD	Observation (if tumor small and asymptomatic) Surgical resection if embolization has occurred (must ensure complete valve inspection because not infrequently multiple—as high as 21%) [40] May require valvular repair or replacement
RHABDOMYOMAS			
Approx 20% of all primary cardiac tumors Exclusively in children but can occur in adults (8.5%) Accounts for approx. 20% of primary cardiac tumors 90% associated with Tuberous Sclerosis (*TSC1/TSC2* mutations, autosomal dominant) and associated with "ash-leaf" cutaneous macules	Most cases present in the first year of life Associated with **Pringle's disease**: (1) Tuberous sclerosis (80–90%) (2) Adenoma sebaceum of the skin (3) Kidney tumors Found in ventricular walls or atrioventricular valves as it develops from within the myocardium (intramural) or endocardium May be pedunculated Occurs in multiples more commonly in the right ventricle than in the left (90%) Firm white lobules ranging from few millimeters to centimeters Rhabdomyomas on TTE are smooth-margined and project into cardiac chamber with subtle T2 hyperintensity on LGE slightly greater than surrounding myocardium	Heart failure due to obstruction to circulation Arrhythmias ie tachyarrhythmias due to invasion of cardiac conduction system or AV block Pericardial effusion Sudden death	Regress spontaneously with age (50%) Surgical removal even in asymptomatic individuals even in symptom free Anticoagulation therapy may be indicated

TABLE 28-6

(CONTINUED)

INCIDENCE	CHARACTERISTICS	COMPLICATIONS	MANAGEMENT
FIBROMAS			
Rare but second most common primary cardiac tumor in children 4% occurrence in adults 3–5% associated with Gorlin Syndrome—*PTCH1* mutation, associated with basal cell carcinomas, skeletal abnormalities, ectopic CNS calcifications [39]	Arise from the myocardium and may occur in any cardiac chamber Usually intramural arising from interventricular septum, left ventricle, endocardium or valves (most common) May develop in response to inflammation Usually solitary and can become large (3–10 cm) Do not regress spontaneously Often mistaken for hypertrophic cardiomyopathy or apical thrombus On TTE, Fibromas usually bright myocardial mass with areas of hyperintensity due to focal microcalcification	Heart failure due to obstruction to circulation Arrhythmias (and SCD) by compressing or invading conduction system Atypical chest pain	Surgical resection (total or partial; subtotal is preferred to spare vital structures, since these tumors rarely recur) Cardiac transplantation if tumor is too large to be resected
HEMANGIOMAS			
Approx. 5–10% of benign tumors Affects all ages	Can be multiple (30%)	Usually asymptomatic Can cause SCD or cardiac dysfunction (displaces large portions of atria and ventricles) Can develop recurrent thrombocytopenia, consumptive coagulopathy (Kasabach-Merritt syndrome)	Surgical excision (complete if possible)
HAMARTOMAS			
Affects young children—60% of cardiac tumors in children	Resembles HCM but has localized masses or multiple discrete masses Usually in the RA or RV	Incessant ventricular tachycardia Obstructive symptoms	Surgical excision

TABLE 28-7

INTRACARDIAC MALIGNANT PRIMARY TUMORS, THEIR CHARACTERISTICS AND MANAGEMENT

INCIDENCE	CHARACTERISTICS	COMPLICATIONS	MANAGEMENT
SARCOMAS			
Most common primary malignant neoplasms in the heart Extremely rare Almost all malignant cardiac tumors are sarcomas Affects men > women (65–75%), mean age 47 [41]	>80% of sarcomas involve LA, but arise from posterior wall, unlikely myxomas which arise from IAS **Angiosarcomas** = most occur in RA or right AV groove (80%) or pericardium, can present with continuous murmur, heart failure, tamponade, vena caval obstruction (usually T2 hyperintense with superficial enhancement with variability due to necrosis or hemorrhage) **Rhabdomyosarcomas** = occurs in <20 years of age in any cardiac chamber; may be multiple	Heart failure due to obstruction to circulation Embolic phenomena Arrhythmias Angiosarcomas can also cause catastrophic hemorrhage with tamponade Death	Palliative (course is rapid) Surgical excision Chemotherapy (typically anthracycline-based for sarcomas, paclitaxel may have benefit in angiosarcomas [42] Median survival of high-grade sarcomas are 15 months after resection versus 5 months if extent precluded resection [43]
PRIMARY CARDIAC LYMPHOMA			
1–2% of all cardiac neoplasms Majority are B-cell neoplasms (DLBCL) that may be seen in immune-competent or—compromised hosts (i.e. Burkitt's, EBV-associated, post-cardiac transplant)	Usually involve right-sided chambers and pericardium usually presenting as pericardial masses invading adjacent myocardium Constitutional symptoms Symptoms of direct extension or tumor embolization Avid contrast enhancement on cMRI		Chemotherapy determined by tumor type

TABLE 28-8

EXTRACARDIAC BENIGN PRIMARY TUMORS, THEIR CHARACTERISTICS AND MANAGEMENT

INCIDENCE	CHARACTERISTICS	COMPLICATIONS	MANAGEMENT
THYMOMAS			
	Arise within the pericardium but not from cardiac tissues	Causes tamponade	Surgical removal
TERATOMAS			
Infants	Often attached to the base of the great vessels Tumor arising from pericardium Located in the anterior mediastinum (90%) or posterior mediastinum	Usually asymptomatic	Surgical removal if symptomatic May require urgent pericardiocentesis if causing tamponade
MESOTHELIOMA			
50% of all pericardial tumors	Usually present with constrictive features		Survival <6 months Pericardiectomy can be undertaken palliatively but overall poor prognosis

QUESTIONS AND ANSWERS

1. A 42-year old female with a history some weight loss and increasing fatigue presents with night time coughing spells that wake her up. Her blood pressure is 120/60 mmHg, the pulse is 95 beats per min. Her cardiac examination revealed an early diastolic sound with a mid diastolic low-pitched rumbling murmur at the apex and a presystolic crescendo murmur.

   The most common primary tumor of the heart is:

   a) Fibroma
   b) Papillary Fibroelastoma
   c) Myxoma
   d) Mesothelioma
   e) Sarcoma

1. Answer: c. Myxoma is the most common primary cardiac tumor. Presentation can vary depending on tumor size and location. The classic presentation is a female, 30–50 years of age (through it can present at any age). Classic symptoms of myxoma include constitutional symptoms, evidence of cardiac obstruction and thromboembolic events. Myxomas are usually located in the left atrium over 80% of the time. In this patient with a left atrial tumor, it can obstruct the mitral valve apparatus; thus simulate mitral stenosis on physical exam. It can also cause heart failure symptoms [33].

2. A 72-year old male with a history of lung cancer was found to have a cardiac tumor on a CT scan. What is a true statement?

   a) The most common cardiac tumor is myxoma
   b) The most common cardiac tumor is likely to be from a metastatic disease.

2. Answer: b. Tumors found in the heart are more commonly from metastatic disease. The most common PRIMARY cardiac tumor is myxoma. Tumors with multiple distant metastases that show preferential cardiac involvement include melanoma, bronchioalveolar carcinoma and renal carcinoma [30].

3. The most common presentation for cardiac myxoma is:

   a) Endocarditis
   b) Constitutional symptoms (fatigue or malaise)
   c) Cerebrovascular accident from tumor embolus
   d) Peripheral edema
   e) Syncope

3. Answer: b. Constitutional symptoms such as fatigue, malaise, weight loss, low-grade fever and vague pain are the most common presenting symptoms.

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CHAPTER 29

EMILY S. LAU AND DANITA Y. SANBORN

Imaging Studies Section (Echocardiograms and Angiograms)

CHAPTER OUTLINE

ABBREVIATIONS

A3C	Apical 3 chamber or apical long axis
A4C	Apical 4 chamber
A5C	Apical 5 chamber
Ao	Aorta
ASD	Atrial septal defect
AV	Aortic valve
CW	Continuous wave
DT	Deceleration time
Ef	Effusion
HOCM	Hypertrophic obstructive cardiomyopathy
LA	Left atrium
LAD	Left anterior descending artery
LAO	Left anterior oblique
LCx	Left circumflex coronary artery
LIMA	Left internal mammary artery
LM	Left main coronary artery
LV	Left ventricle
LVOT	Left ventricular outflow track
MR	Mitral regurgitation
MV	Mitral valve
OM	Obtuse marginal
PA	Pulmonary artery
PFO	Patent foramen ovale
PLAX	Parasternal long axis
PSAX	Parasternal short axis
Pulm	Pulmonary
PW	Pulsed wave
RA	Right atrium
RAO	Right anterior oblique
RCA	Right coronary artery
RPA	Right pulmonary artery
RV	Right ventricle
RVOT	Right ventricular outflow track
SAM	Systolic anterior motion

SVG	Saphenous vein graft
TEE	Transesophageal echo
ToF	Tetralogy of Fallot
TTE	Transthoracic echo
TV	Tricuspid valve
VSD	Ventricular septal defect

ECHOCARDIOGRAMS

1. Hypertrophic obstructive cardiomyopathy (Fig. 29-1)
2. RV and RA mass/thrombus (Fig. 29-2)
3. Hypereosinophilic syndrome (Fig. 29-3)
4. Flail anterior MV leaflet (Fig. 29-4)
5. Bileaflet MV prolapse (Fig. 29-5)
6. Rheumatic mitral stenosis (Fig. 29-6)
7. LV apical aneurysm (Fig. 29-7)
8. LV pseudoaneurysm (Fig. 29-8)
9. Secundum atrial septal defect (Fig. 29-9)
10. Carcinoid (Fig. 29-10)
11. MV endocarditis (Fig. 29-11)
12. Coarctation (Fig. 29-12)

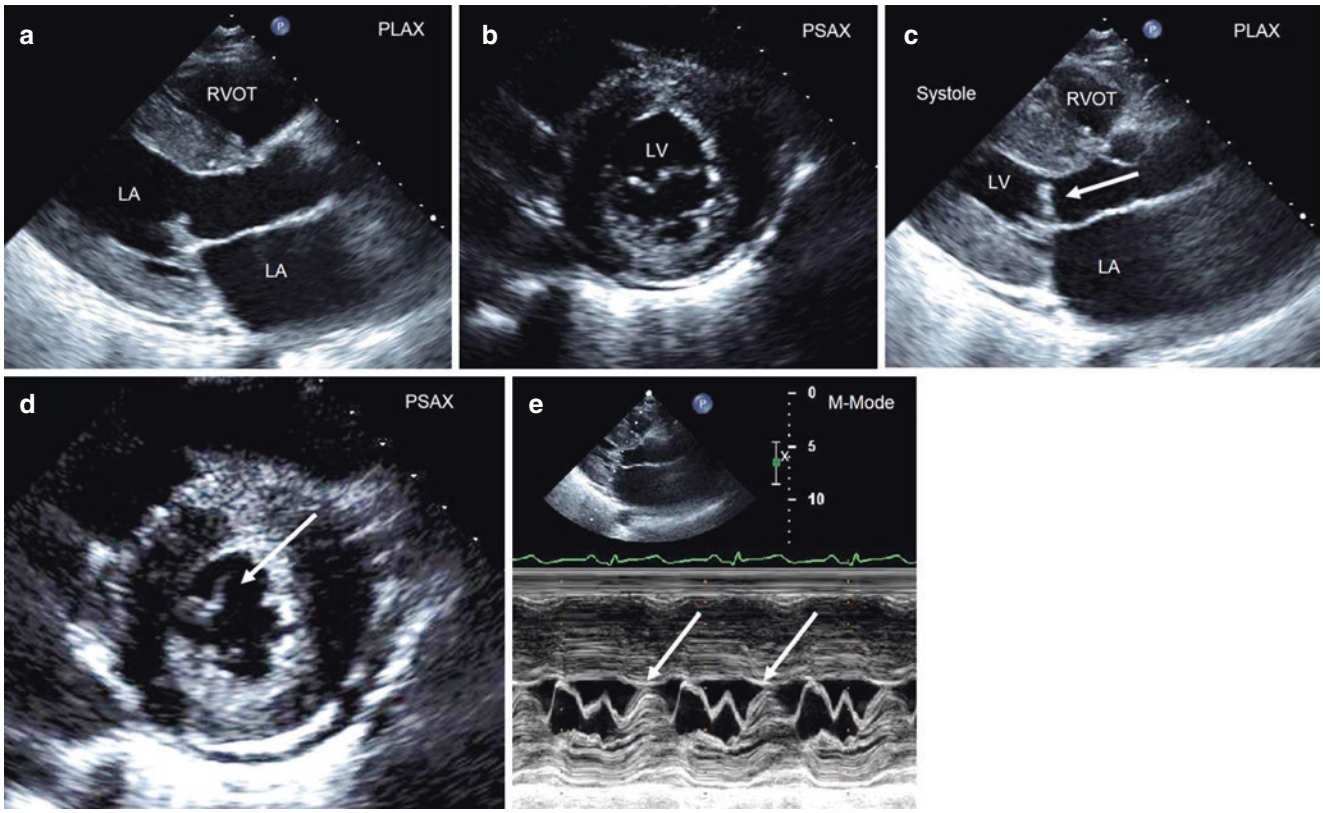


FIGURE 29-1

A 30-year-old woman with shortness of breath and chest burning. HOCM. 2D TTE. Asymmetric septal hypertrophy seen on PLAX (**a**) and PSAX (**b**) views. Panel (**c**, **d**) showing SAM in PLAX and PSAX (arrows) views. SAM also evident by MMode in panel (**e**). *Key Findings: Asymmetric septal hypertrophy. LVOT obstruction/SAM, hypertrophic cardiomyopathy. Complete coding (in addition to above). Normal LV size. Normal WM. Normal to hyperdynamic (LVEF ≥ 50%)*

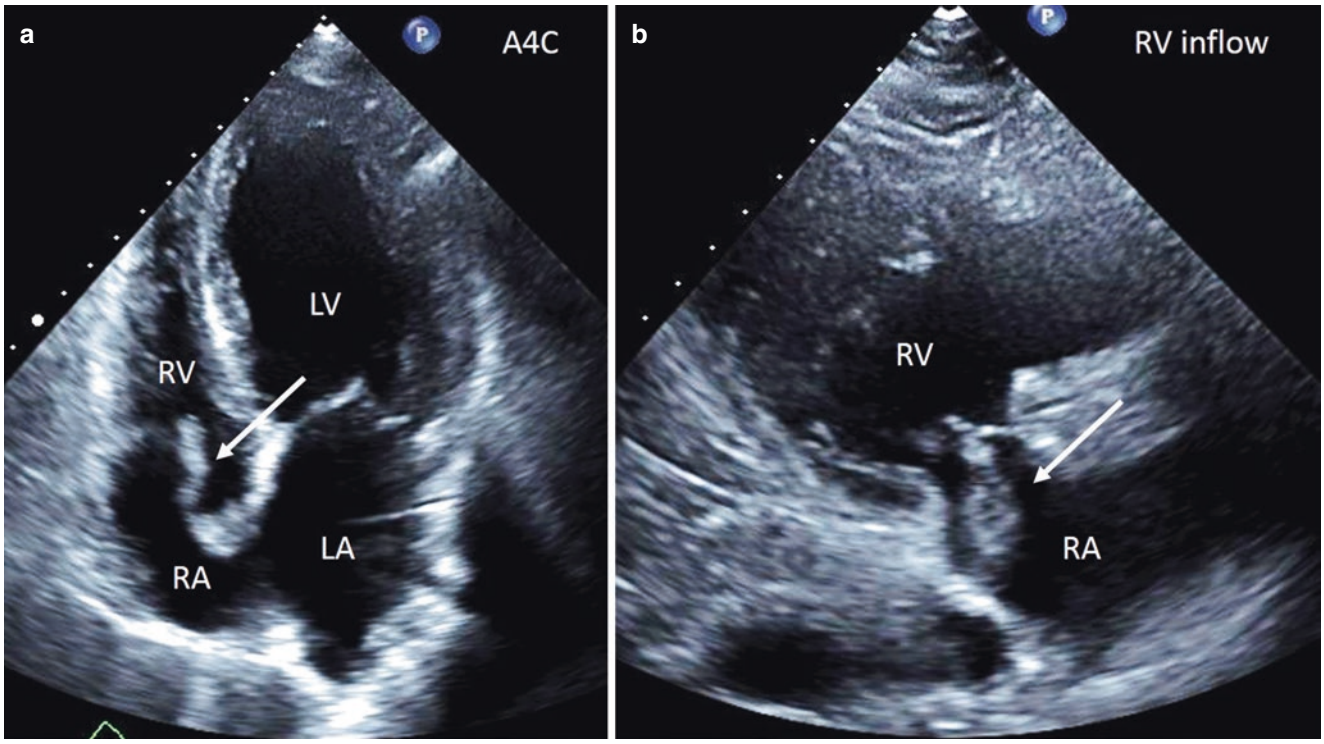


FIGURE 29-2

A 76-year-old woman presents with syncope. RA/RV thrombus. 2D TTE. A large thrombus (arrow) traverses the tricuspid valve seen on A4C view (**a**) and RV inflow view (**b**). *Key Findings: RV mass or thrombus. Atrial thrombus*

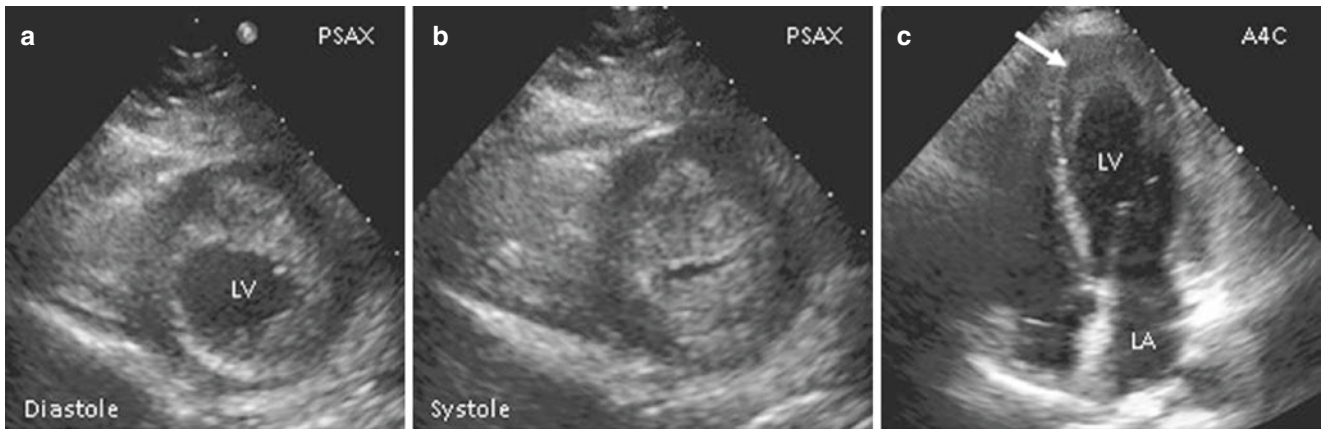


FIGURE 29-3

A 45-year-old man with eczema and dyspnea. Hypereosinophilic syndrome. 2D TTE. PSAX in diastole (**a**) and systole (**b**) with significant LV soft tissue/eosinophils and thrombus deposition (arrow) at the apex of the heart (usually obliterating the apex), and no underlying wall motion abnormality. Panel (**c**) showing apical 4 chamber view of the same process. Make sure to be able to differentiate this from apical hypertrophic cardiomyopathy (which maintains a slitlike opening in the apex). *Key Findings: LV Mass or Thrombus. Hypereosinophilia*

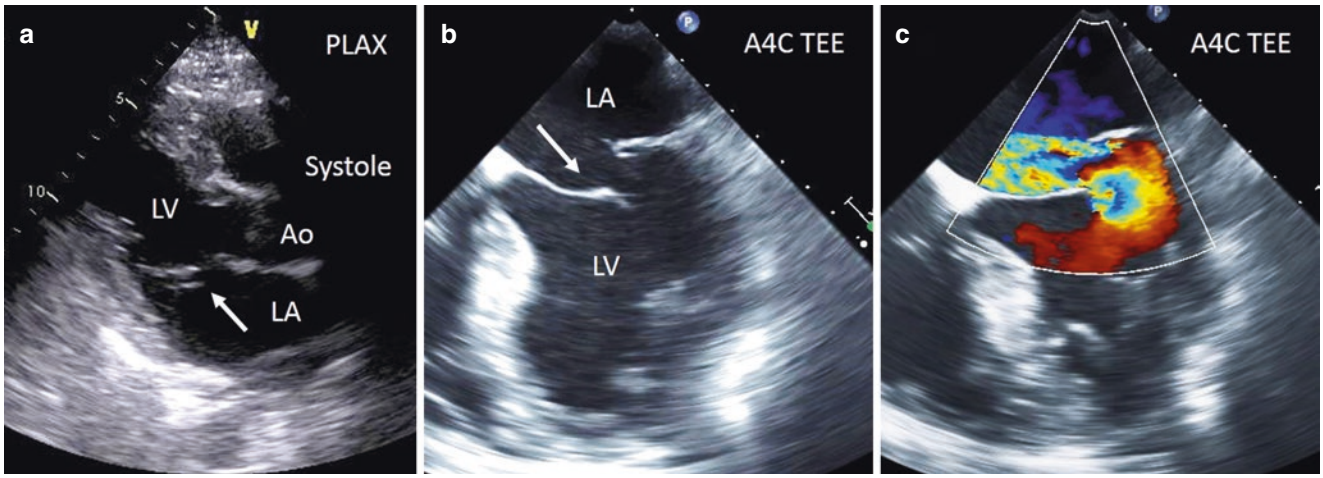


FIGURE 29-4

A 63-year-old man with cough, fatigue, and dyspnea. Flail MV leaflet. 2D TTE. PLAX view (**a**) showing posterior mitral valve leaflet flail (arrow). 2D TEE. Apical 4 chamber view showing flail posterior mitral valve leaflet (**b**, arrow) and severe eccentric MR resulting from flail posterior MV leaflet (**c**). *Key Findings: Flail MV. Severe MR. Enlarged LA*

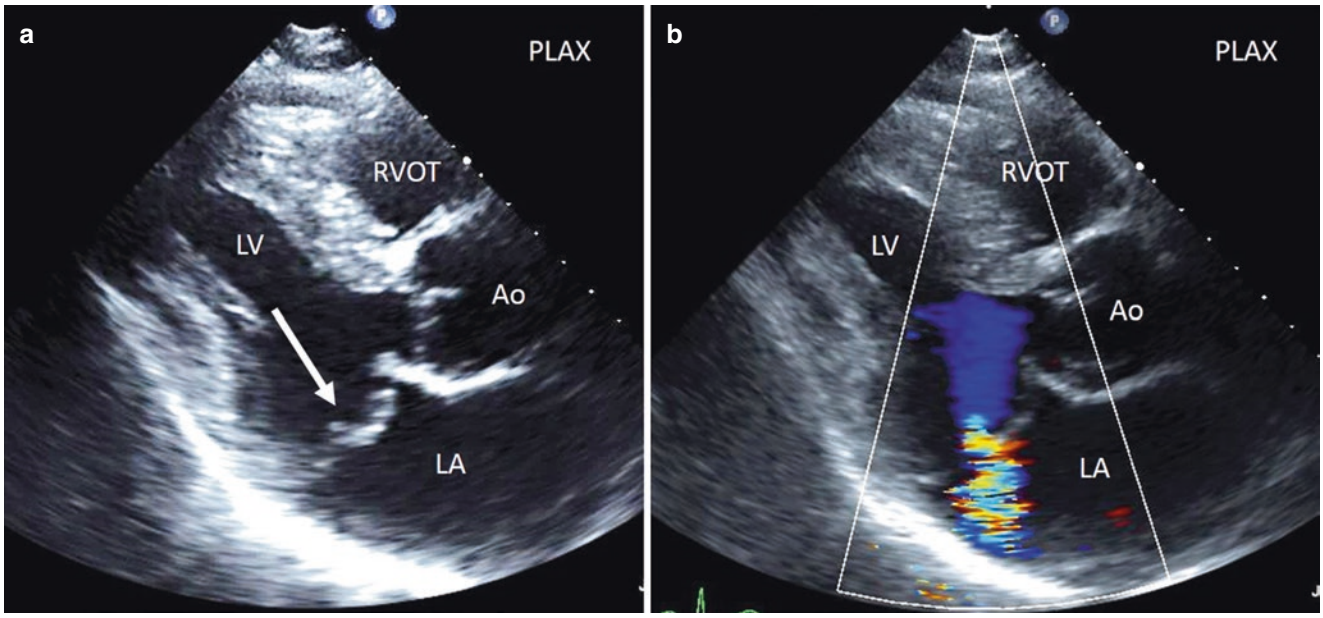


FIGURE 29-5

A 67-year-old man with a holosystolic murmur. Bileaflet MV prolapse. 2D TTE. PLAX view (**a**) showing bileaflet prolapse (arrow). The anterior leaflet is preferentially affected, resulting in a posteriorly directed jet of MR seen by color Doppler (**b**). *Key Findings: MV prolapse. Moderate MR. Enlarged right/left atrium*

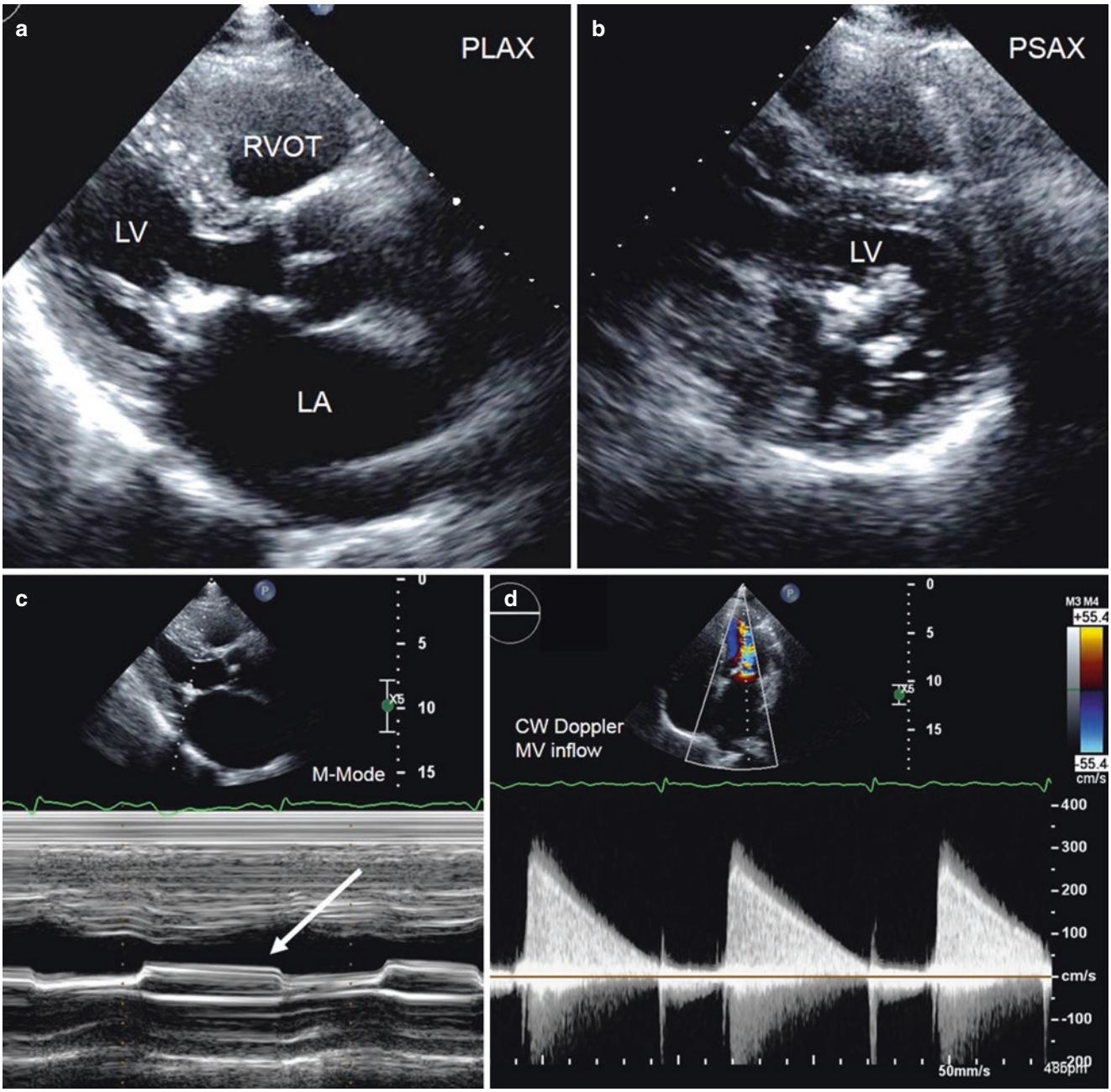


FIGURE 29-6

A 74-year-old man from China with weight loss and shortness of breath. Rheumatic mitral stenosis. 2D TTE. PLAX view (**a**) showing thickened MV leaflet tips in a domed appearance and the anterior mitral valve leaflet with "hockey stick" appearance (arrow). Panel (**a**) shows a dilated LA. PSAX view (**b**) in diastole showing a restricted MV orifice which can be planimetered to provide a mitral valve area. Panel (**c**) is a MMODE tracing showing thickened MV leaflets (arrow) with reduced excursion. Panel (**d**) is a transmitral continuous wave (CW) Doppler tracing showing a relatively flat pressure decay with elevated transmitral gradients. *Key Findings: Rheumatic MV. Enlarged LA. Severe MV stenosis*

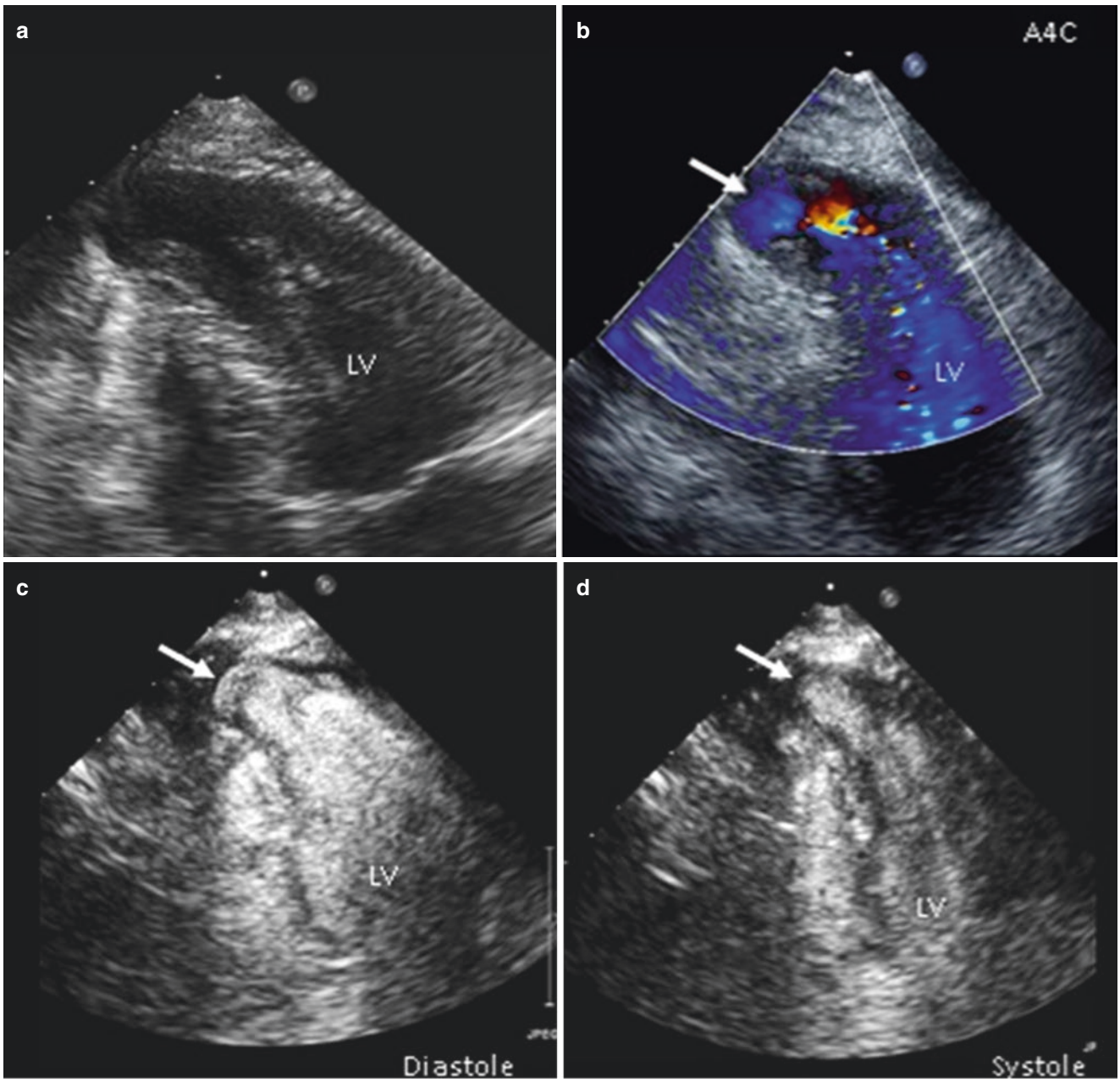
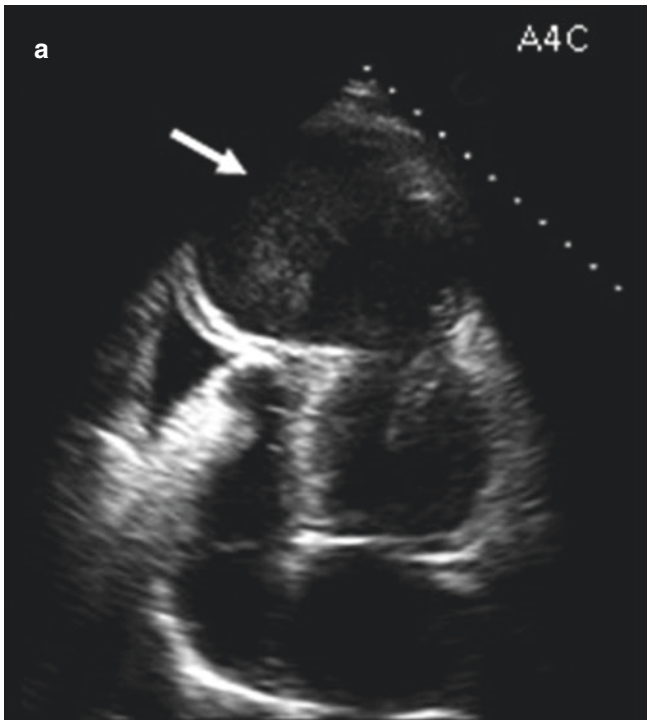


FIGURE 29-7

A 76-year-old man with history of prior infarction. LV apical aneurysm. 2D TTE. Panel (**a**) shows an apical 4 chamber view of the aneurysm with color Doppler flow (**b**) into the aneurysm (arrow). Diastolic (**c**) and systolic (**d**) frames with LV contrast clearly show myocardial contraction in the aneurysmal segment (arrows). *Key Findings: Apical aneurysm*



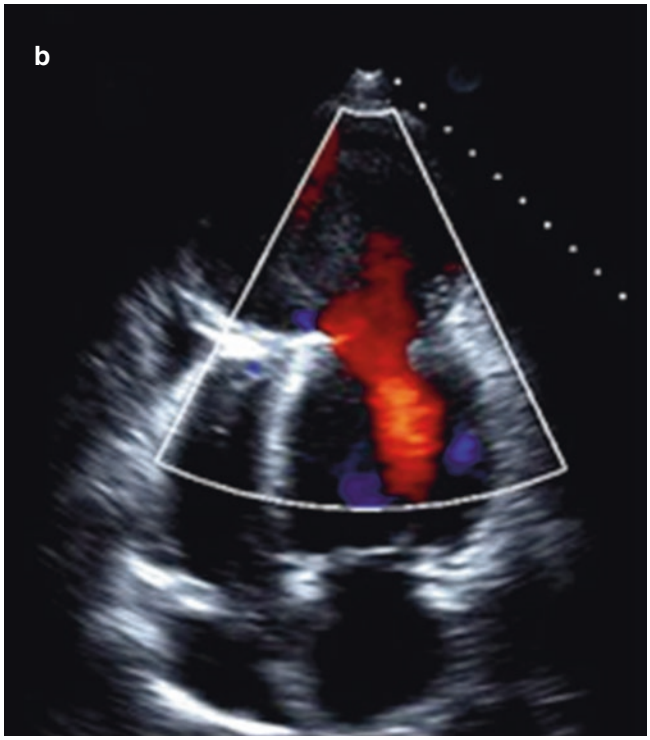


FIGURE 29-8

A 75-year-old woman with coronary artery disease. LV pseudoaneurysm. 2D TTE. Panel (**a**) shows an apical 4 chamber view at end systole with a large (72 mm × 73 mm) akinetic space containing spontaneous echo contrast at the apex of the LV suggestive of pseudoaneurysm (arrows). Panel (**b**) shows color Doppler with flow into the pseudoaneurysm. *Key Findings: Apical pseudoaneurysm*

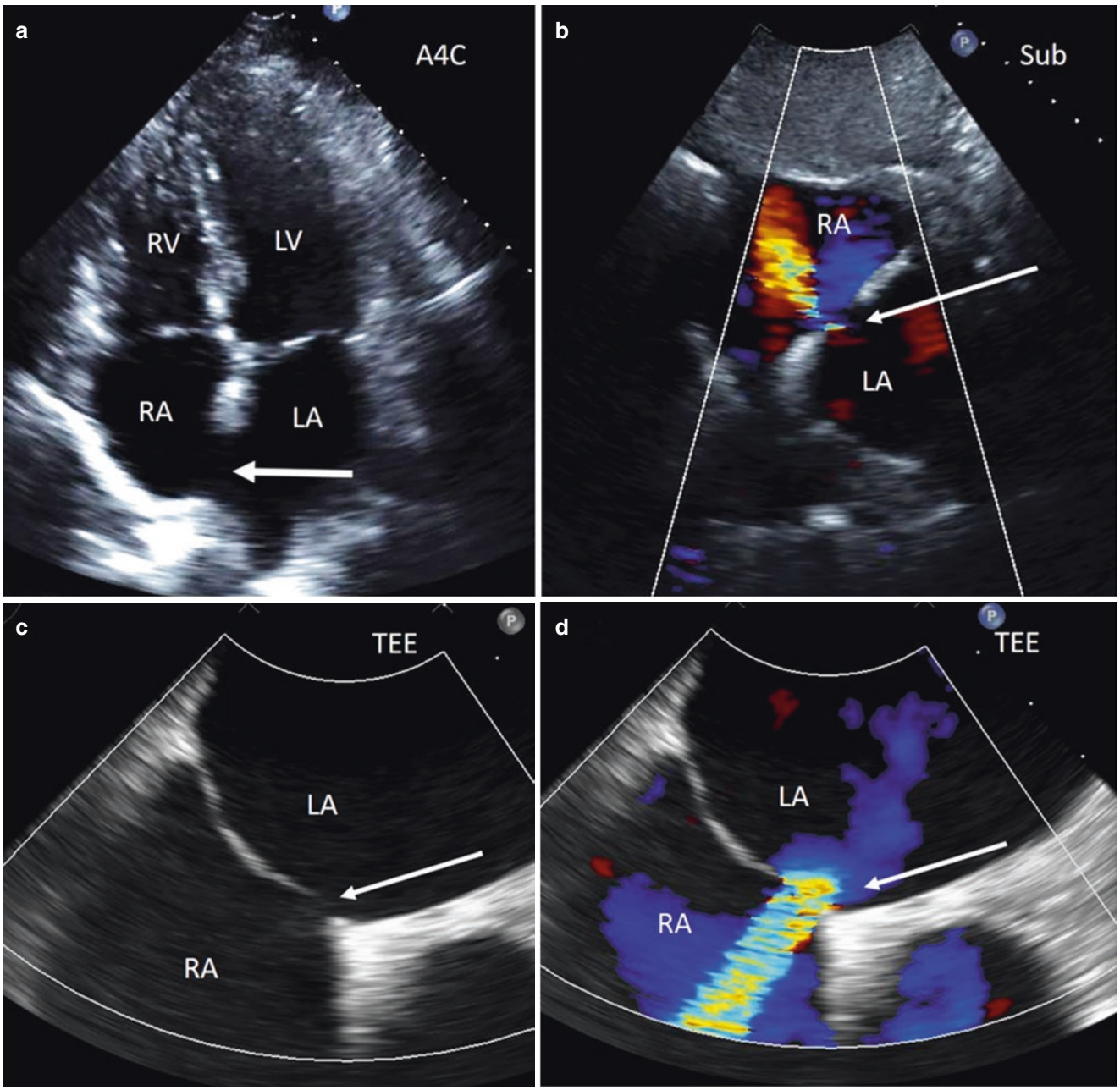


FIGURE 29-9

A 68-year-old man with exertional dyspnea. Secundum atrial septal defect. 2D TTE. Apical 4 chamber view (**a**) of a defect in the mid-interatrial septum consistent with a secundum ASD. Subcostal view (**b**) with color Doppler confirms left to right flow across the defect. 2D TEE. Mid-esophageal 4 chamber 2D and color Doppler views (**c**, **d**) further characterize the lesion. *Key Findings: Secundum ASD. Enlarged RA*

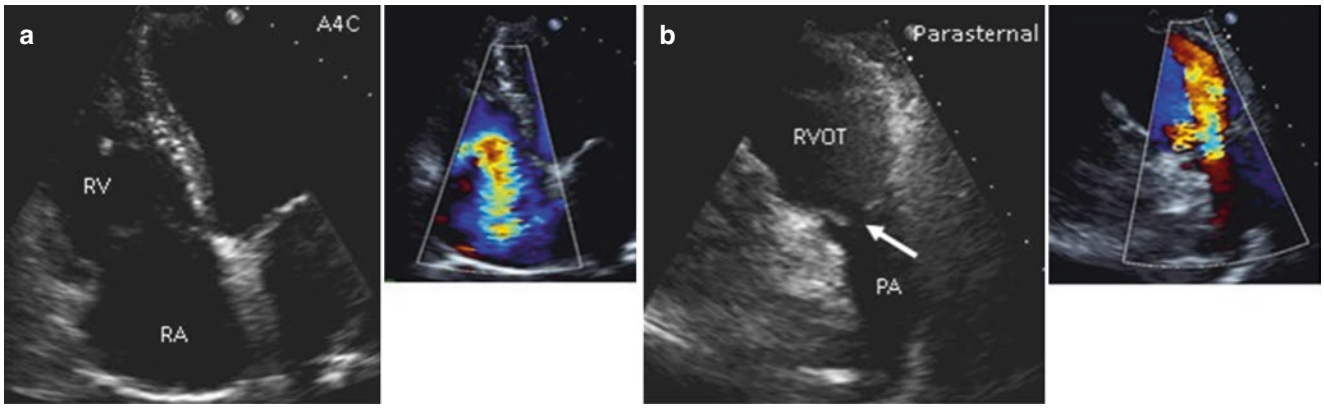


FIGURE 29-10

A 65-year-old man with lower extremity edema and elevated liver enzymes. Carcinoid. 2D TTE. Apical 4 chamber view (**a**) systolic frame showing thickened TV leaflets with failure of coaptation resulting in severe TR seen by color Doppler. Parasternal view (**b**) showing pulmonary valve (arrow) involvement and leaflet thickening resulting in severe pulmonary insufficiency. *Key Findings: Enlarged RA. TV carcinoid. Severe TR. PV carcinoid. Severe PR*

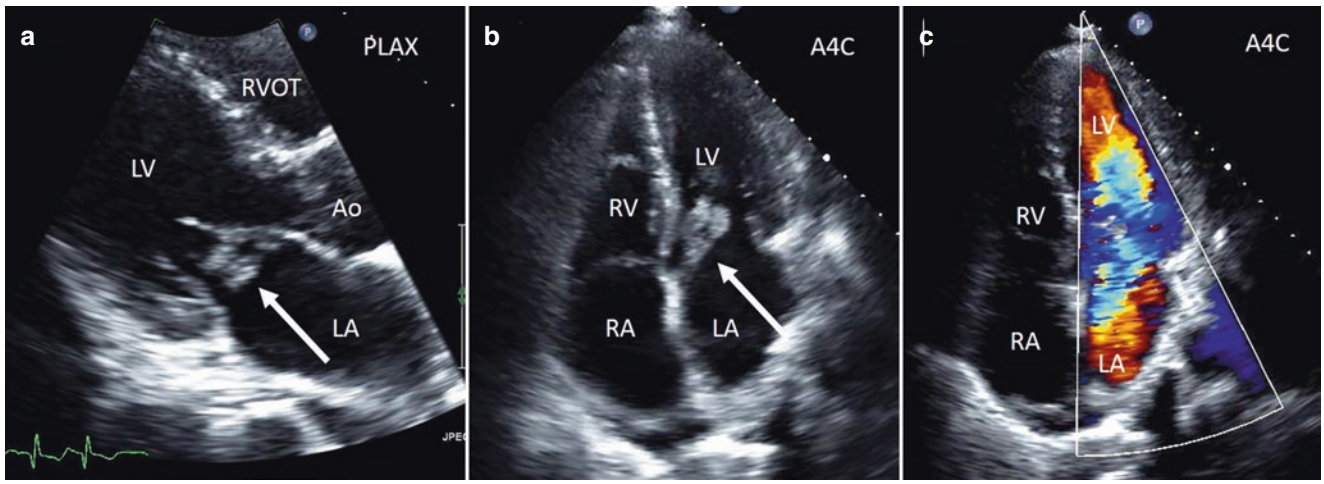


FIGURE 29-11

A 69-year-old man with shortness of breath. Mitral valve endocarditis. 2D TTE. PLAX view (**a**) and Apical 4 chamber view (**b**) show a mobile mass of echoes attached to the anterior mitral valve leaflet, consistent with vegetation. (**c**) Apical 4 chamber view with color Doppler shows severe mitral regurgitation. *Key Findings: MV vegetation. Severe MR*

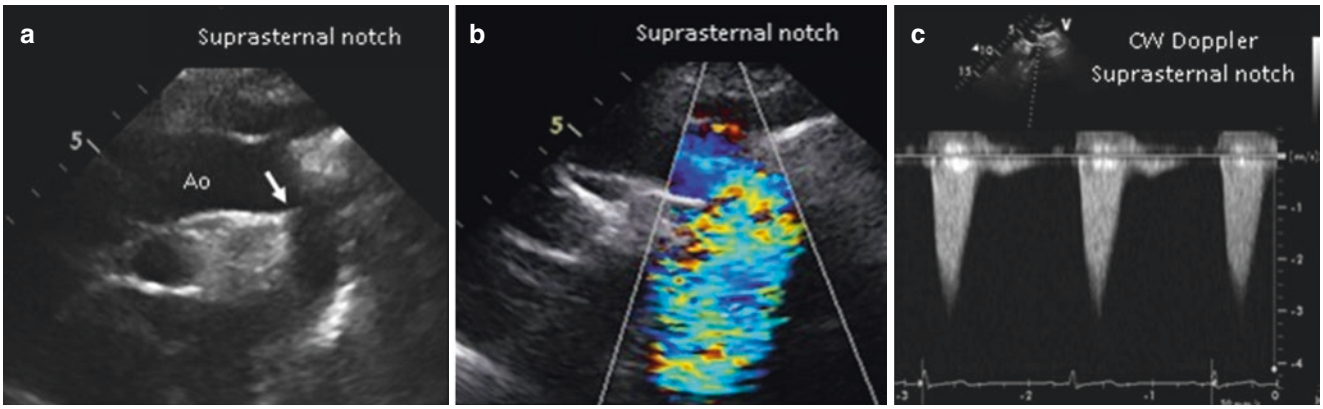


FIGURE 29-12

A 30-year-old man with unequal blood pressures in his arms. Aortic coarctation. 2D TTE. Suprasternal notch view (**a**) showing a shelf-like narrowing of the aorta (arrow) resulting in flow acceleration and flow turbulence seen by color Doppler (**b**). CW across the coarct (**c**) quantifies the flow acceleration and estimates the pressure gradient that is generated. *Key Findings: Coarctation*

13. Patent ductus arteriosus (Fig. 29-13)
14. Noncompaction (Fig. 29-14)
15. Ventricular septal defect (Fig. 29-15)
16. Dilated cardiomyopathy (Fig. 29-16)
17. Subaortic stenosis (Fig. 29-17)
18. LV thrombus (Fig. 29-18)
19. Tamponade (Fig. 29-19)
20. Aortic valve, tri, bi, unicuspid (Fig. 29-20)
21. Papillary fibroelastoma and lipomatous hypertrophy of the interatrial septum (Fig. 29-21)
22. Myocardial infarction (Fig. 29-22)
23. Atrial myxoma (Fig. 29-23)
24. Cardiac amyloidosis (Fig. 29-24)
25. Ebstein's anomaly (Fig. 29-25)
26. Takotsubo (stress-induced) cardiomyopathy (Fig. 29-26)
27. Pulmonary embolism (Fig. 29-27)
28. Aortic dissection (Fig. 29-28)
29. Mechanical AV Dehiscence (Fig. 29-29)
30. Mitral valve cleft (Fig. 29-30)
31. Tetralogy of Fallot (Fig. 29-31)

ANGIOGRAMS

1. Myocardial bridge and an LAD to PA fistula (Fig. 29-32)
2. Coronary dissection (Fig. 29-33)
3. Coronary vasospasm and air embolism (Fig. 29-34)
4. Coronary thrombus (Fig. 29-35)
5. Coronary aneurysm and severe ectasia (Fig. 29-36)
6. Patent LIMA bypass graft (Fig. 29-37)
7. Left-to-right collateral blood flow (Fig. 29-38)
8. Patent and occluded stents (Fig. 29-39)
9. Anomalousc coronary artery (Fig. 29-40)
10. Three vessel coronary artery disease (Fig. 29-41)

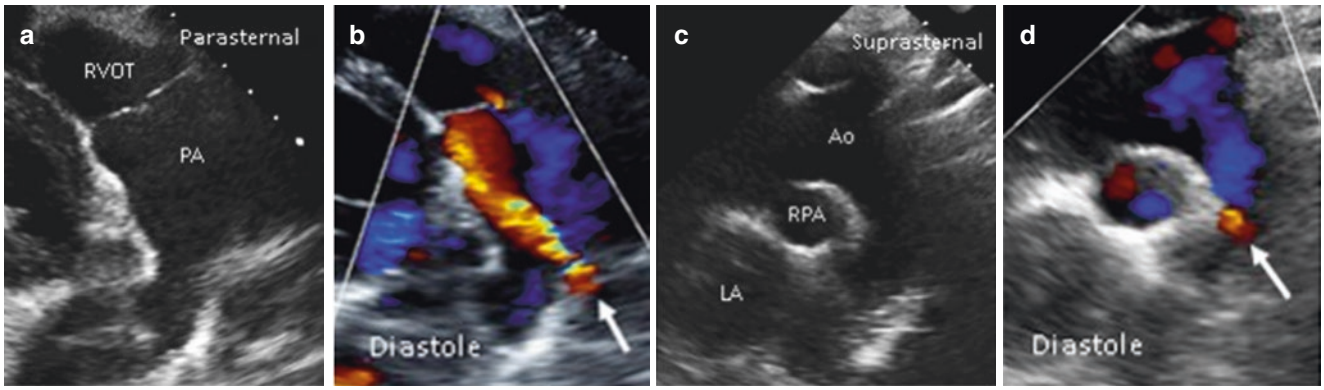


FIGURE 29-13

A 12-year-old boy with a continuous murmur. Patent ductus arteriosus. 2D TTE. Parasternal view of the main pulmonary artery (**a**) with color Doppler (**b**) showing diastolic flow (arrow) into the vessel. Suprasternal view (**c**) with color Doppler (**d**) showing high velocity diastolic flow originating in the aorta. *Key Findings: PDA*

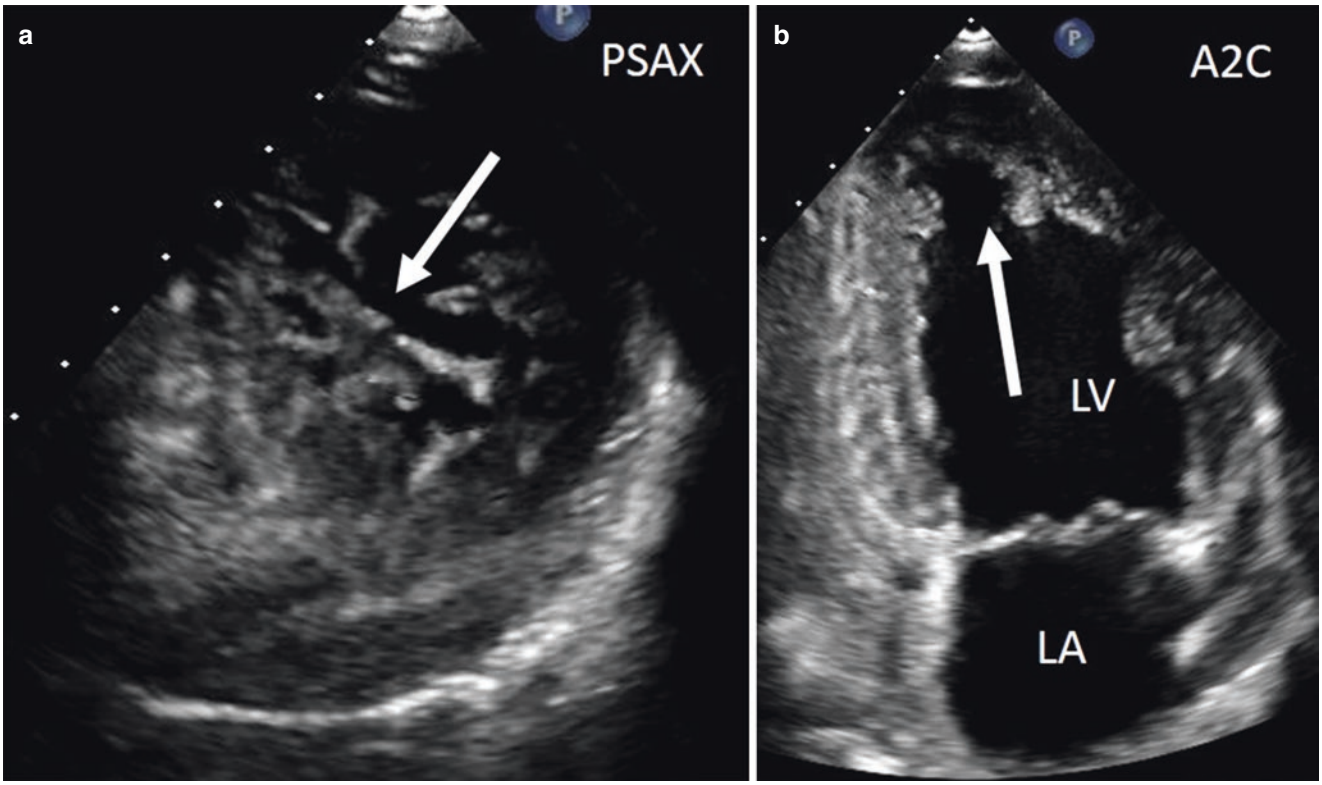


FIGURE 29-14

A 21-year-old man with syncope. LV non-compaction. 2D TTE. PSAX view of the LV apex (**a**) shows a heavily trabeculated (arrows) appearance with intramyocardial sinusoids. Apical 2 chamber view (**b**) shows that the inferolateral LV mid to apical cavity is most affected. *Key Findings: Noncompaction*

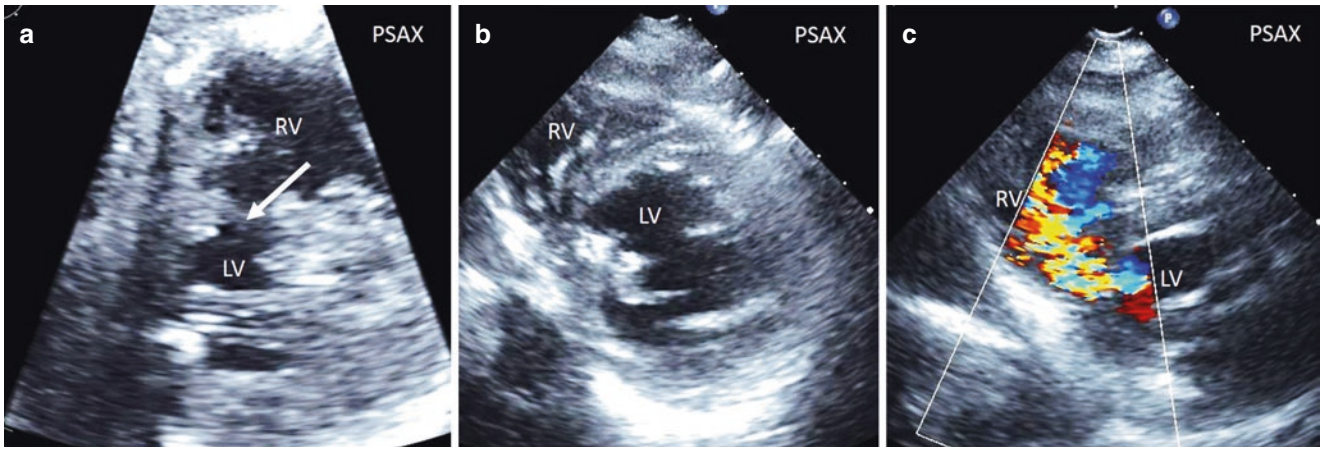


FIGURE 29-15

An 85-year-old woman with 2 days of nausea and vomiting. Ventricular septal defect. 2D TTE. PSAX views (**a**, **b**) show a VSD secondary to LV infarct in the inferior septum (arrow) resulting in high velocity and turbulent flow from the LV to the RV (**c**), seen in the video. Inferorseptal wall motion abnormality evident on PSAX view (**b**). *Key Findings: VSD. Abnormal wall motion abnormality. Inferior/septal akinesis*

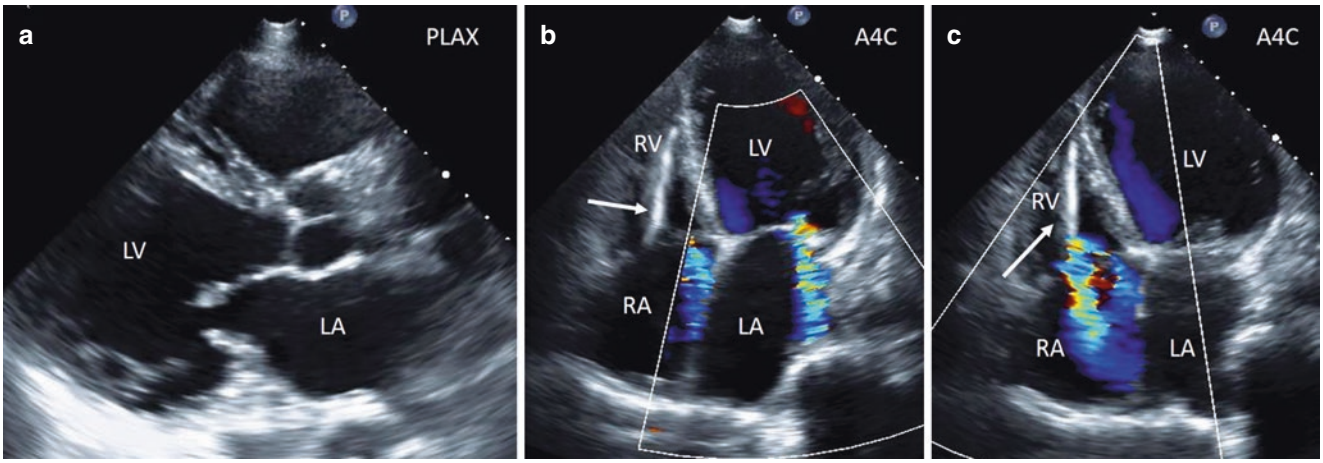


FIGURE 29-16

An 86-year-old woman with lower extremity edema and shortness of breath. Dilated cardiomyopathy. 2D TTE. PLAX view (**a**) shows dilated LV and RV with global hypokinesis. Apical 4 chamber views with color Doppler demonstrated pacemaker lead in the RV and severe functional mitral (**b**) and tricuspid (**c**) regurgitation. *Key Findings: Dilated Cardiomyopathy. Severely reduced (<35%) LV function. Global hypokinesis. Severe MR. Severe TR. Catheter or pacemaker wire*

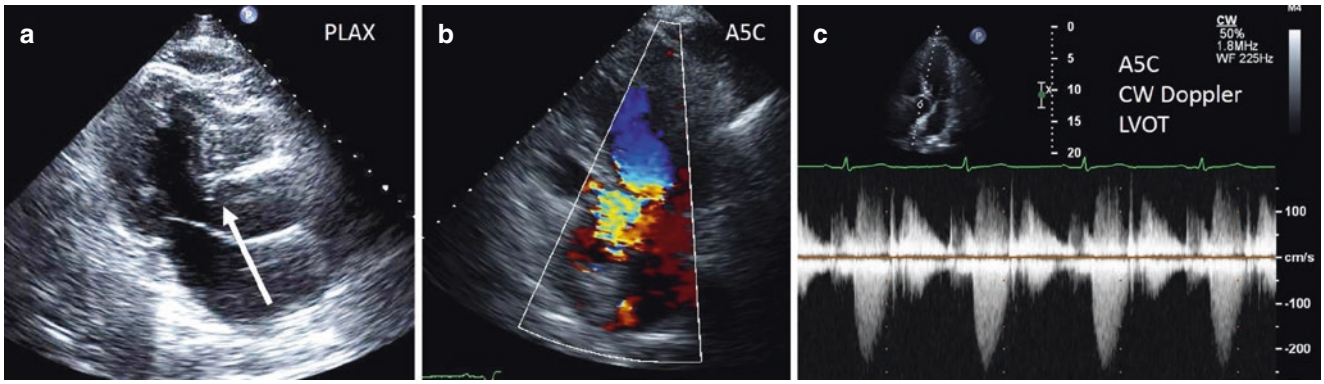


FIGURE 29-17

A 60-year-old man with shortness of breath. Subaortic stenosis. 2D TTE. PLAX view (**a**) of the subaortic membrane (arrow). Apical 5 chamber shows flow acceleration prior to subaortic membrane by color Doppler (**b**) and by CW Doppler at the LV outflow tract (**c**). *Key Findings: Subaortic stenosis*

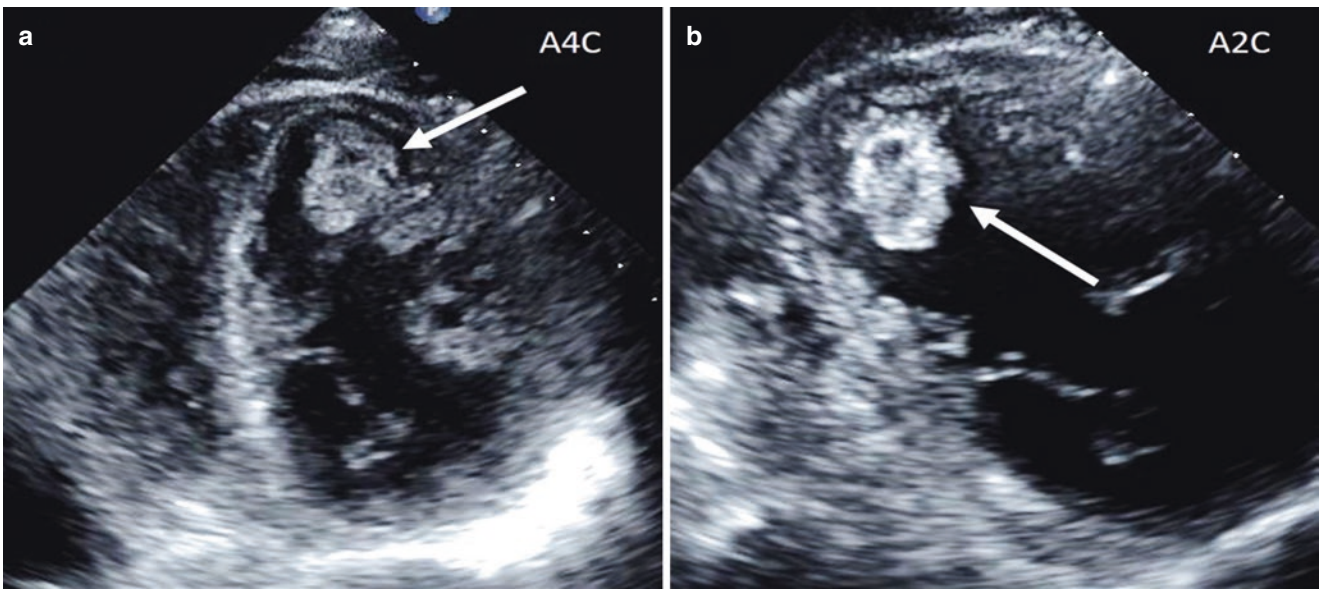


FIGURE 29-18

A 54-year-old man with untreated hypothyroidism presents with new shortness of breath and chest pain. LV thrombus. 2D TTE. Apical 4 chamber (**a**) and apical 2 chamber (**b**) off-axis views show an apical LV thrombus (arrow). *Key Findings: LV mass or thrombus. Global hypokinesis. Severely reduced EF*

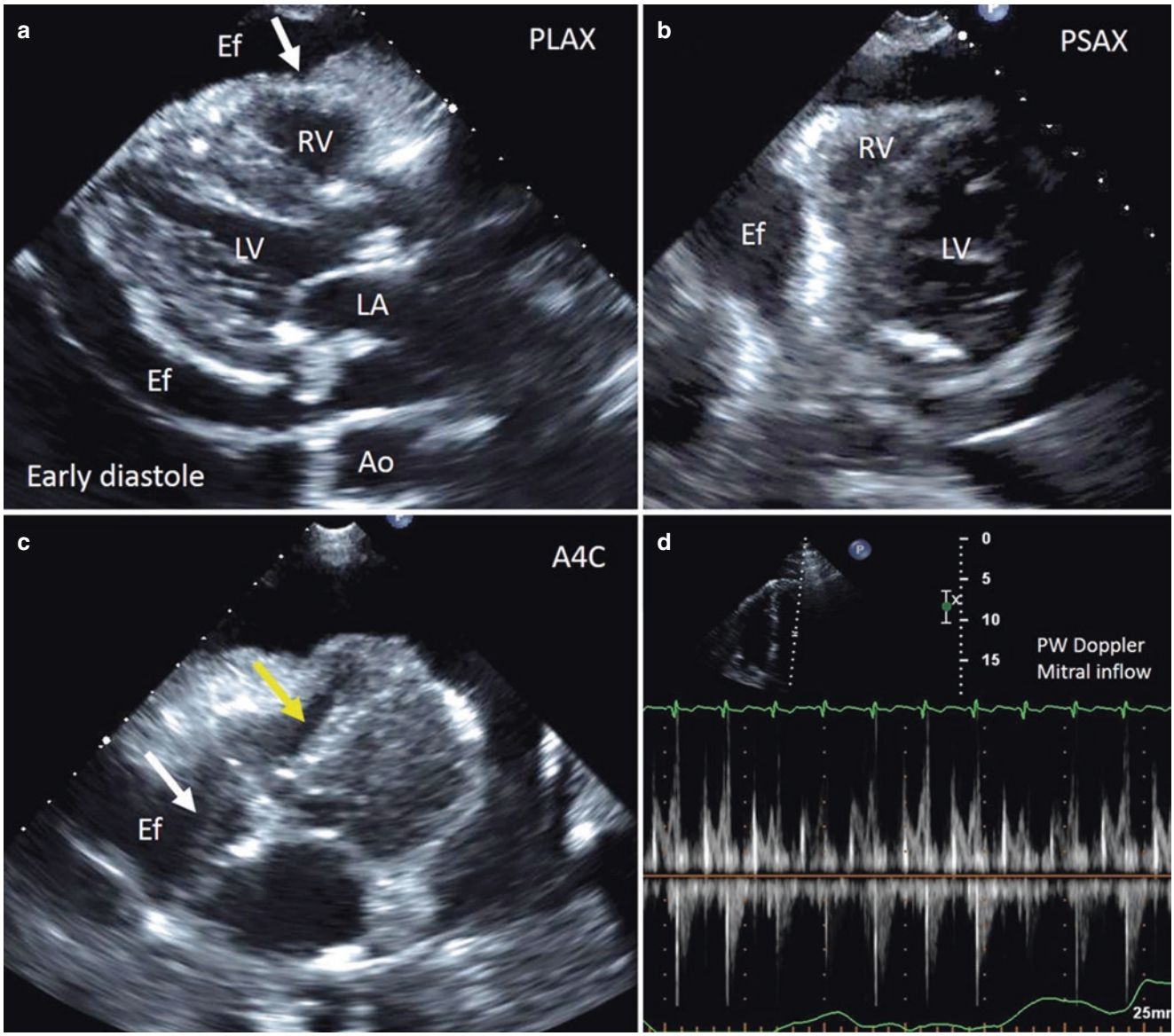


FIGURE 29-19

A 95-year-old woman with hypothyroidism who presents with shortness of breath. Cardiac tamponade. 2D TTE, PLAX (**a**) and PSAX (**b**) showing a large circumferential pericardial effusion with RV inversion (arrow) during early diastole. Apical 4 chamber view (**c**) showing RA (white arrow) and RV (yellow arrow) inversion, and PW Doppler (**d**) at the mitral valve leaflet tips showing respirophasic variation of Doppler flow across the mitral valve. *Key Findings: Pericardial effusion. Pericardial tamponade*

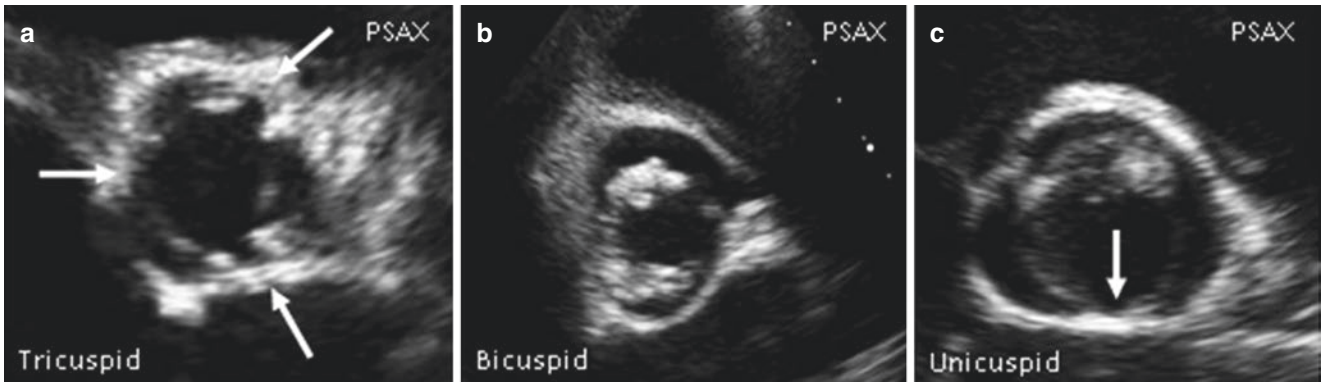


FIGURE 29-20

A 35-year-old with a crescendo-decrescendo systolic ejection murmur. Tricuspid (**a**), Bicuspid (**b**), and Unicuspid (**c**) AV. 2D TTE. PSAX views of the AV in systole. Notable is the elliptical shape of the bicuspid valve orifice in systole as well as the thickened valve leaflets. The unicuspid valve showing only one commissure reaching the annulus at the 6 o'clock position (arrow) whereas the tricuspid valve has all three commissures reaching the annulus (arrows). *Key Findings for figure B: Bicuspid AV*

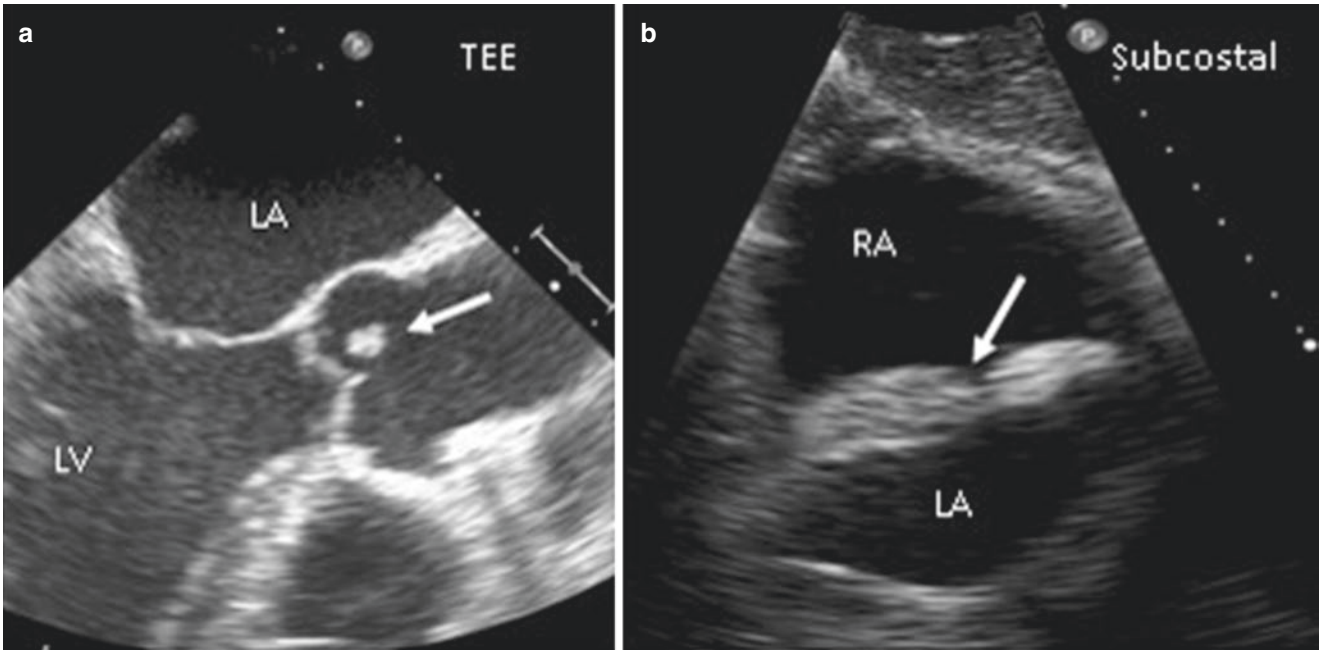


FIGURE 29-21

A 20-year-old woman with an ST elevation infarction. Papillary fibroelastoma (**a**) and Lipomatous hypertrophy of the interatrial septum (**b**). Mid-esophageal TEE long axis view (**a**) of the AV showing a small spherical mass attached via a pedicle to the aortic side of the valve leaflets suspicious for a papillary fibroelastoma. Subcostal view (**b**) by 2D TTE showing lipomatous hypertrophy of the interatrial septum with characteristic sparing (thinning) of the fossa ovalis (arrow). *Key Findings: Fibroelastoma. Atrial septal lipomatous hypertrophy*

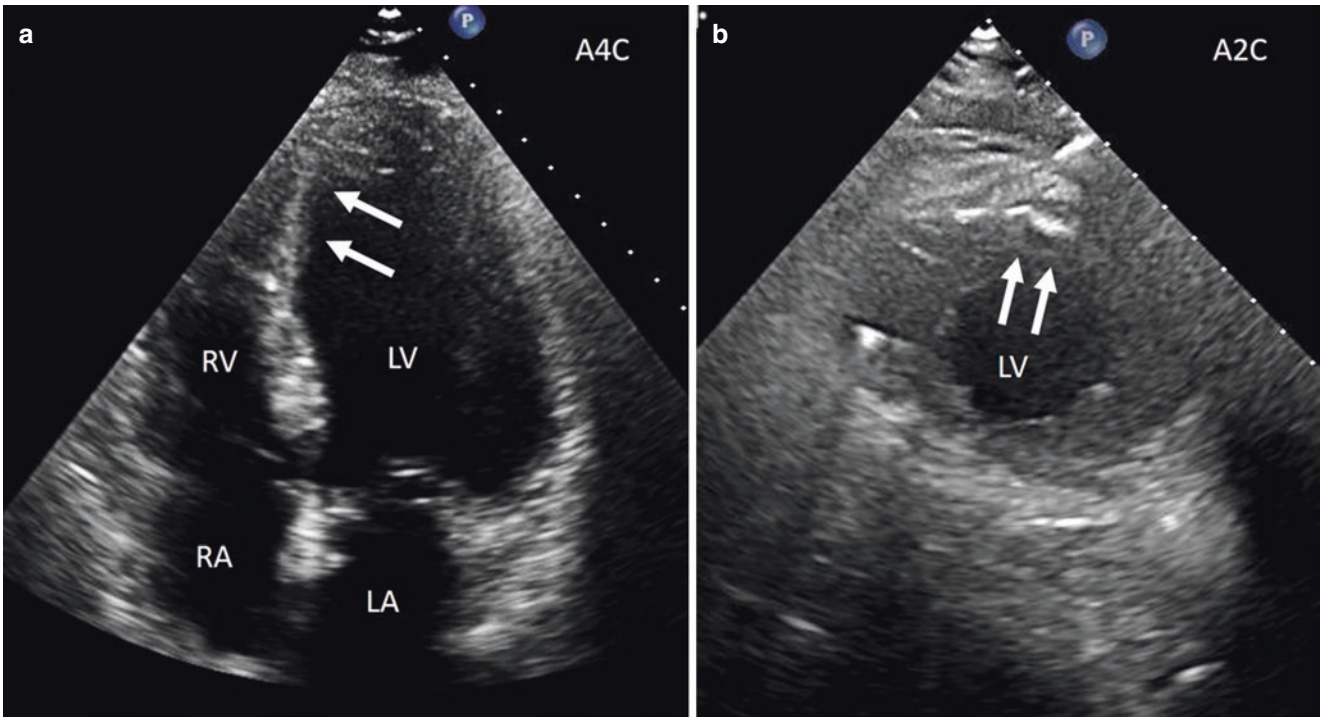


FIGURE 29-22

A 67-year-old man with prior CABG presents with two days of chest pain and shortness of breath. Myocardial scar. 2D TTE apical 4 chamber (**a**) and PSAX view (**b**) showing a thinned and echo-bright septum (arrow) characteristic of scar formation. *Key Findings: Septal thinning and/or scar. Enlarged LV size. Severely reduced LVEF. Abnormal wall motion*

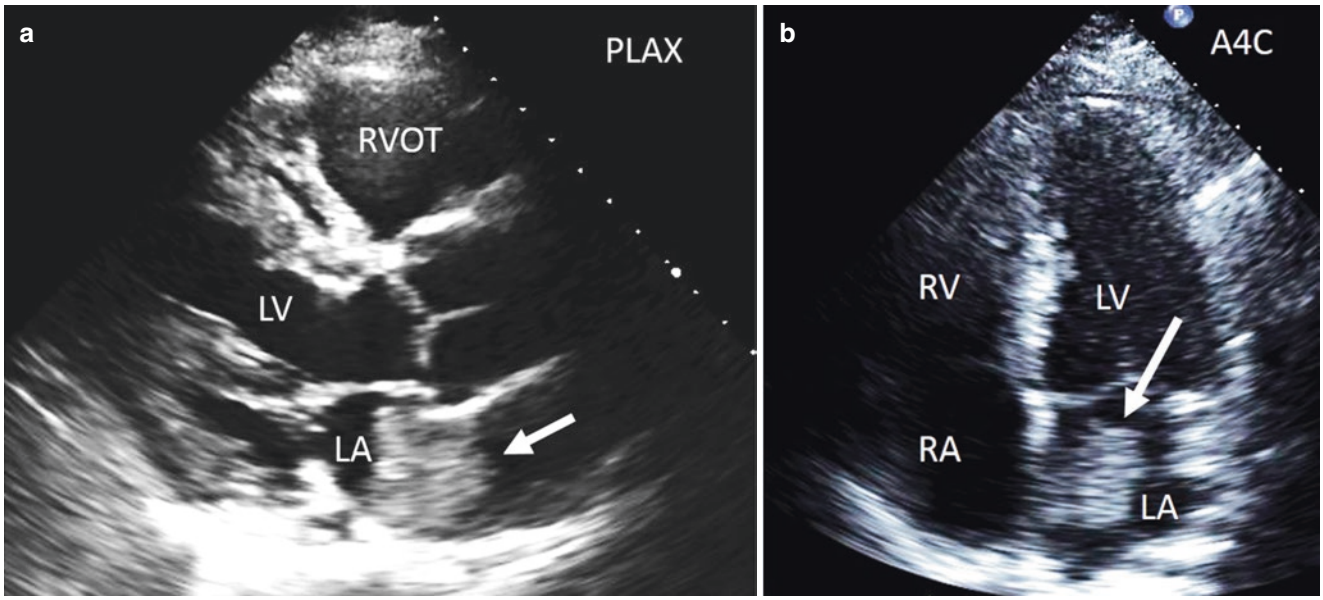


FIGURE 29-23

A 48-year-old man with Carney Complex presents with chest pain. Atrial myxoma. 2D TTE. PLAX view (**a**) and apical 4 chamber view (**b**) of a left atrial myxoma (arrows). *Key Findings: Atrial myxoma*

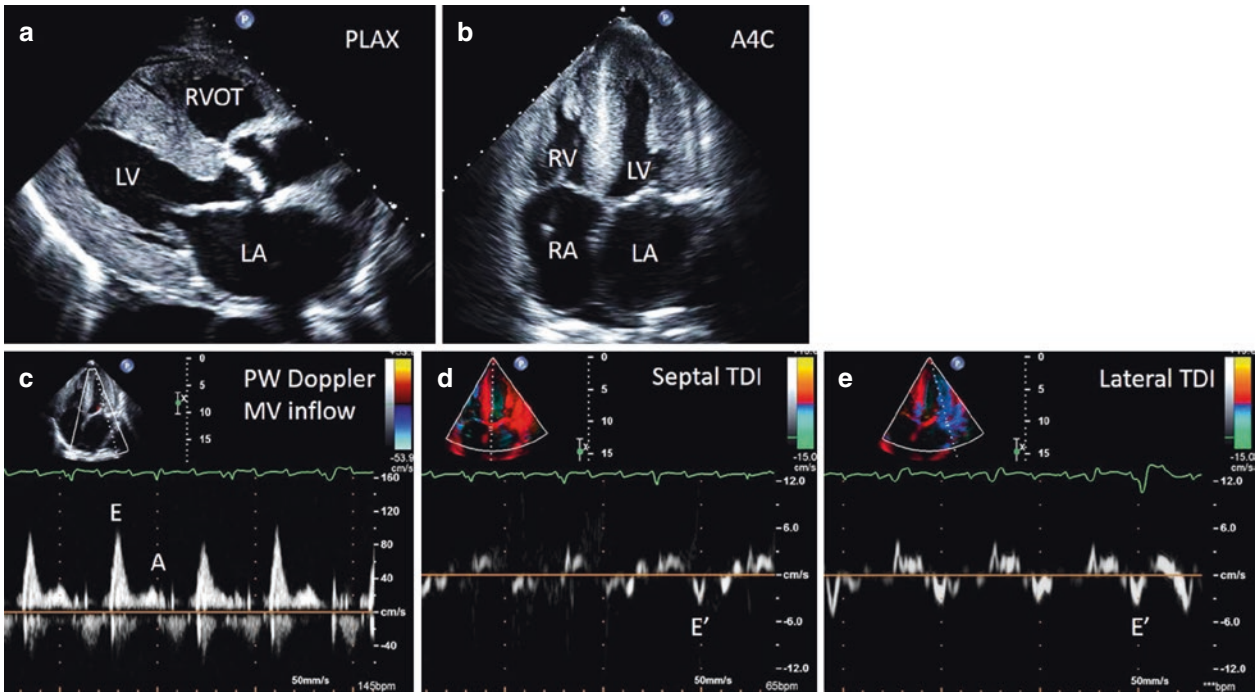


FIGURE 29-24

A 69-year-old man with renal failure and syncope. Cardiac amyloidosis. 2D TTE PLAX (**a**) and Apical 4 chamber (**b**) views show biventricular hypertrophy, increased myocardial reflectivity, as well as biatrial enlargement (**a**, **b**). Panel (**c**–**e**) demonstrate evidence of diastolic dysfunction: E/e′ ratio > 14 (**c**), Septal e′ < 7 cm/s (**d**), and Lateral e′ < 10 cm/s (**e**). *Key Findings: Diastolic dysfunction. Concentric LV wall thickness increase. Enlarged left atrium. Enlarged right atrium. Amyloid*

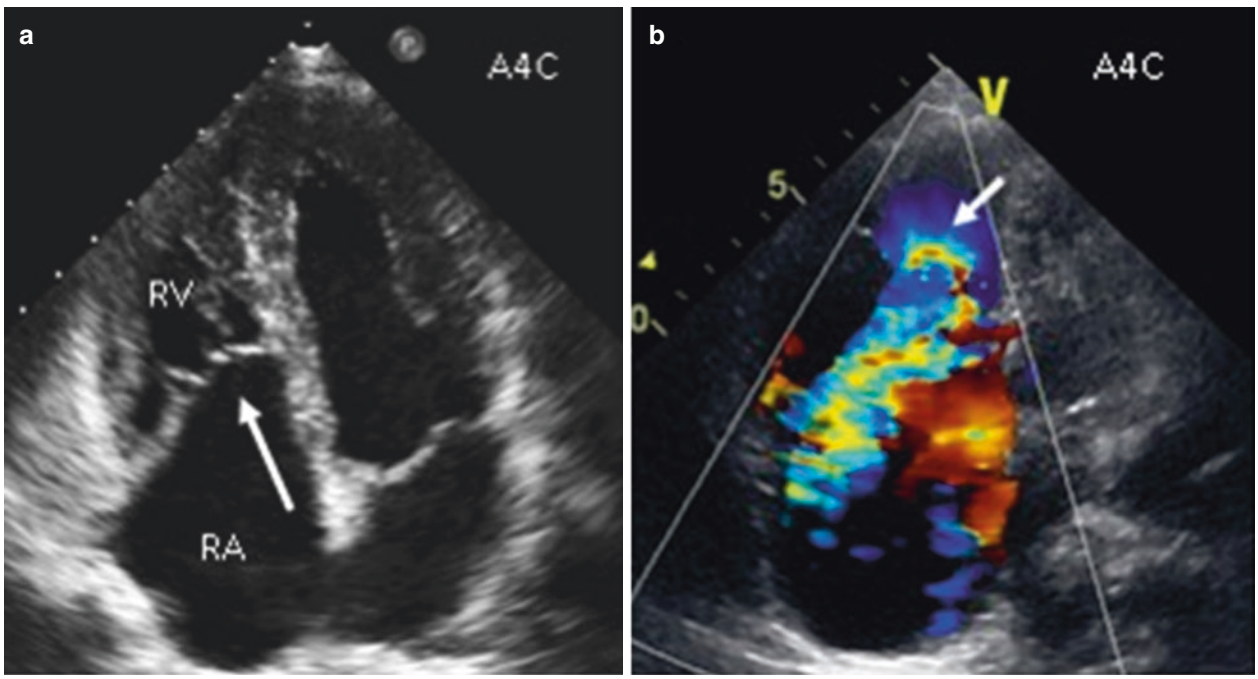


FIGURE 29-25

A 20-year-old woman with palpitations. Ebstein's anomaly. 2D TTE. Apical 4 chamber view (**a**) showing an apically displaced TV (arrow) as compared with the MV annulus resulting in a smaller and distorted true right ventricle as well as a larger and distorted "atrialized" right ventricle. Panel (**b**) is an apical 4 chamber color Doppler of another patient with Ebstein anomaly where the TV is even further apically displaced. Poor coaptation of the leaflets (arrow) results in severe tricuspid regurgitation. *Key Findings: Ebstein's anomaly. Severe TR*

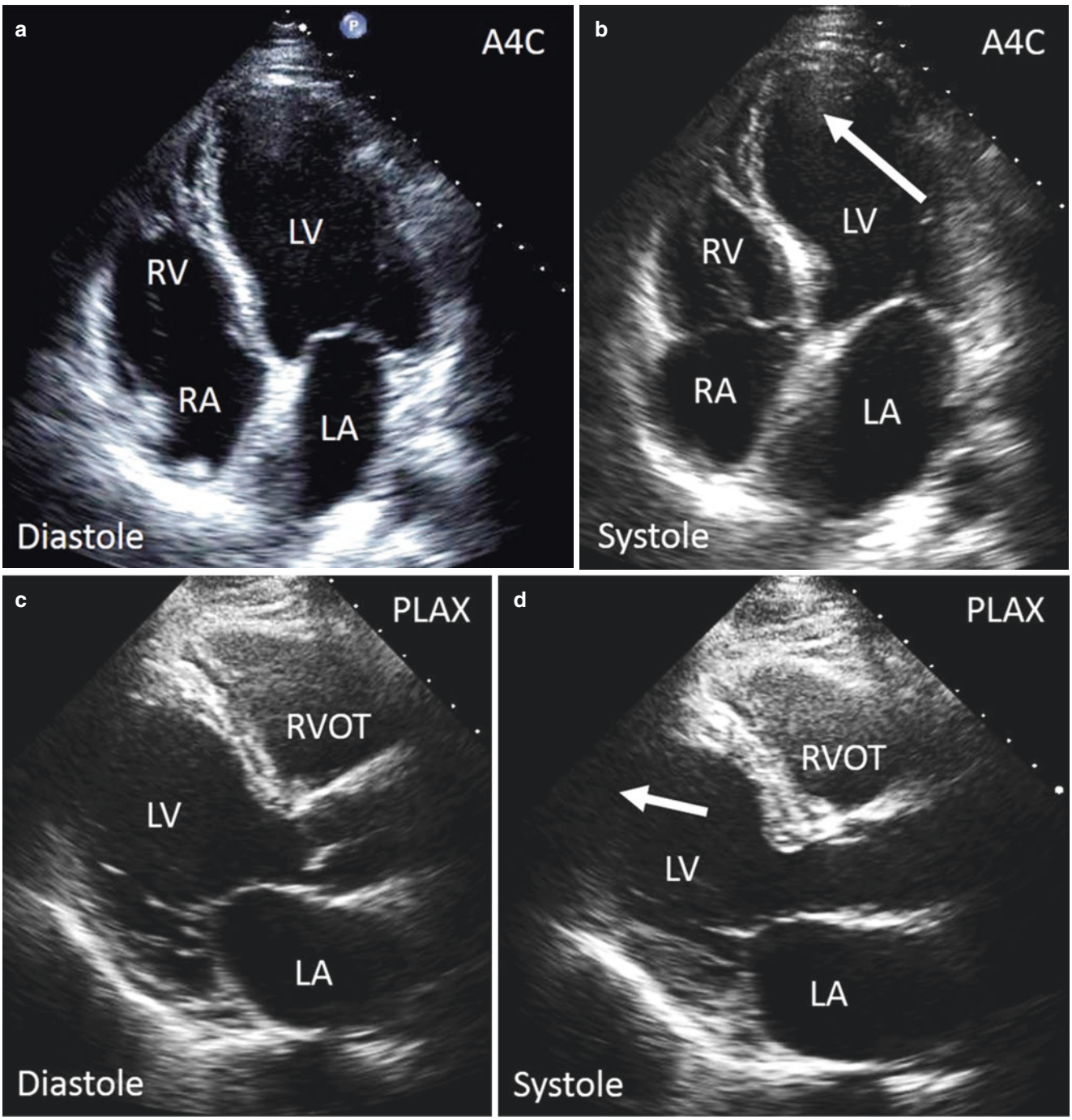


FIGURE 29-26

A 70-year-old woman with chest pain after learning that her daughter was in a motor vehicle accident. Takotsubo (stress-induced) cardiomyopathy. 2D TTE showing an apical 4 chamber diastolic (**a**) and systolic (**b**) frames with apical hypokinesis (arrow) and preserved function at the base. PLAX diastolic (**c**) and systolic (**d**) frames demonstrate vigorous basal LV contraction characteristic of Takotsubo's cardiomyopathy

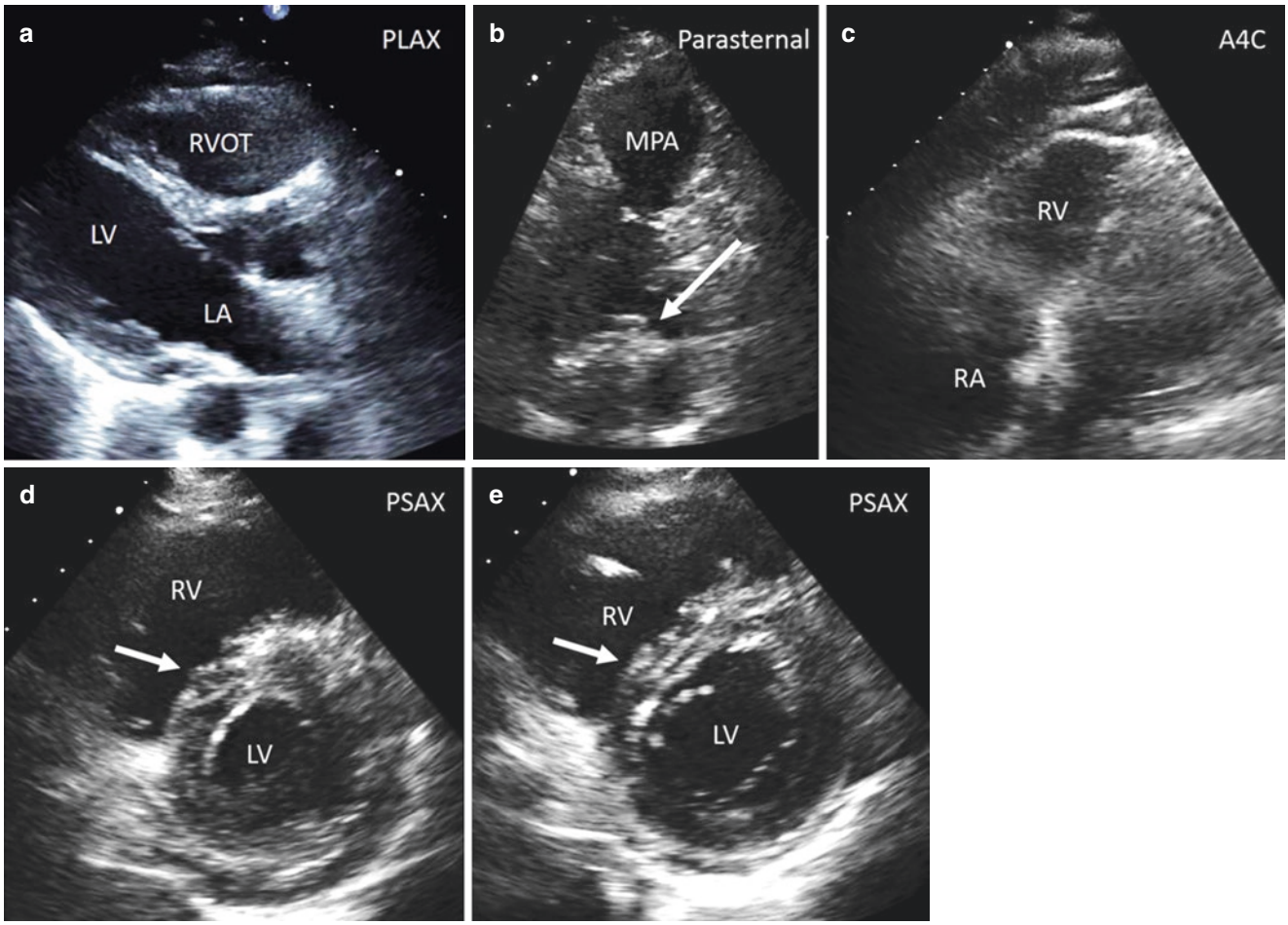


FIGURE 29-27

A 60-year-old woman with cerebellar oligodendroglioma presents with a swollen right leg and shortness of breath. Pulmonary embolism. 2D TTE. PLAX (**b**) show a dilated and hypokinetic RV (Panel **a**). Parasternal view (**b**) of the main pulmonary artery at the bifurcation revealing a saddle pulmonary embolism (arrow). Apical 4 chamber RV focused view (**c**) of McConnell's sign. PSAX view of the LV at end systole (**d**) and end diastole (**e**) showing interventricular septal flattening (arrows) consistent with RV pressure and volume overload. *Key Findings: Findings consistent with acute pulmonary embolism. Global RV dysfunction. Enlarged RV. RV volume overload. RV pressure overload*

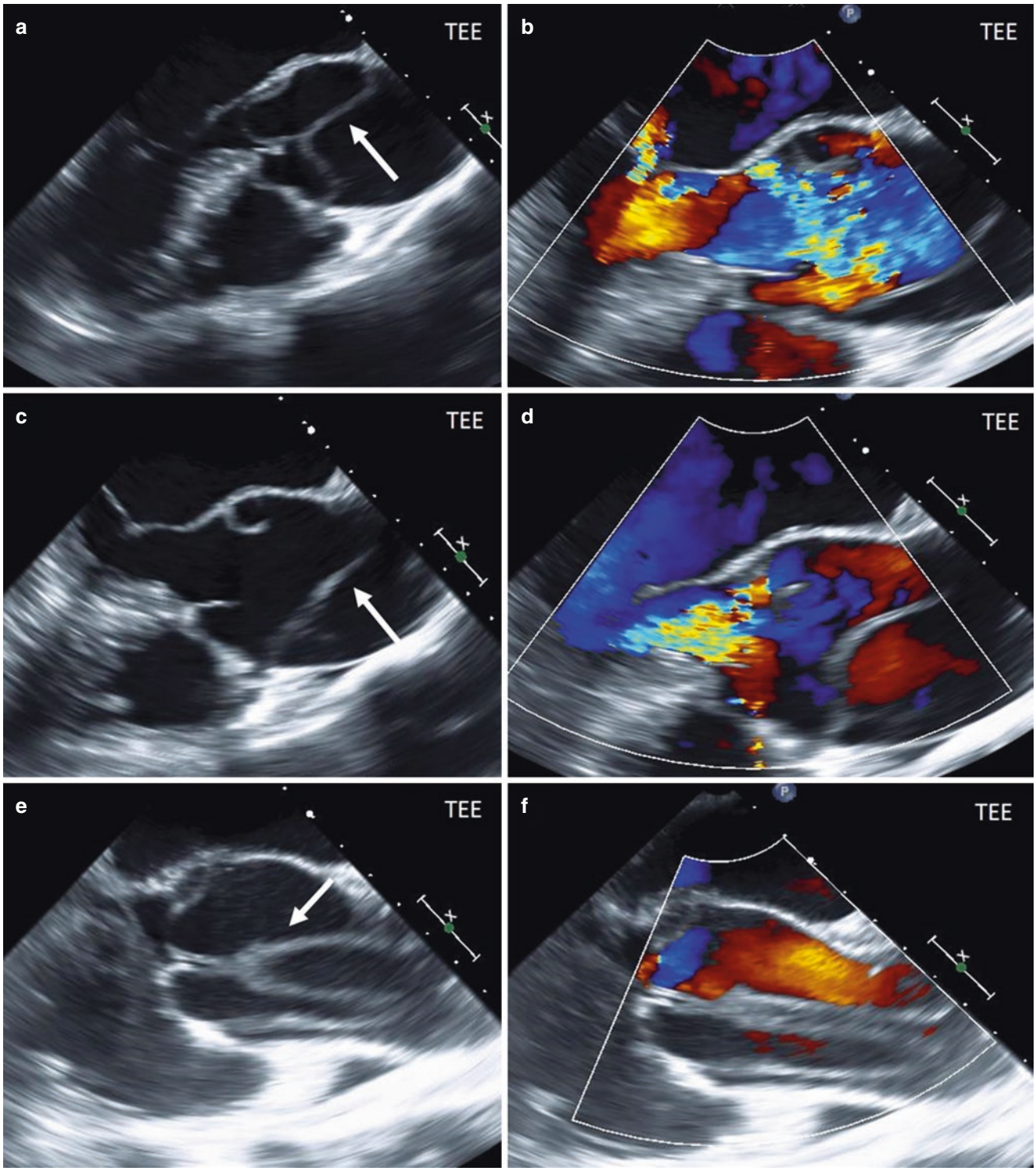


FIGURE 29-28

A 56-year-old man with HTN presents with chest and back pain. Aortic dissection. 2D TEE (**a**, **c**, **e**) showing an enlarged ascending aorta with evidence of a dissection flap (arrow). Color Doppler shows flow in the false lumen (**b**, **d**, **f**) and severe aortic insufficiency (**b**, **d**). *Key Findings: Type A aortic dissection. Aortic enlargement or aneurysm. Severe aortic valve regurgitation*

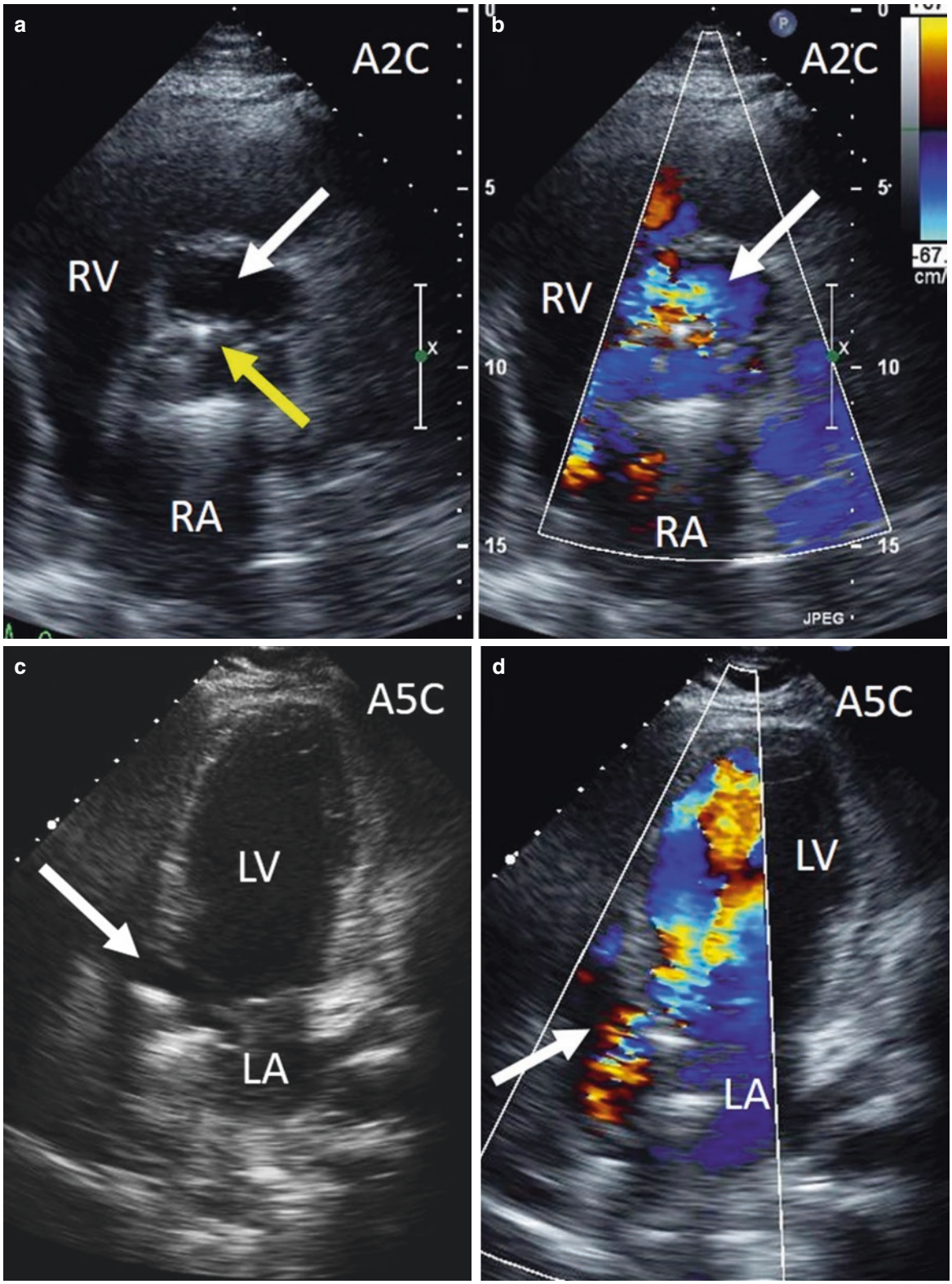


FIGURE 29-29

A 40-year-old man with recent mechanical AVR presents with chest pain 4 weeks post operatively. Mechanical AV Dehiscence. 2D TTE. PSAX view (**a**, **b**) of #27 St. Jude mechanical aortic valve prosthesis. There is a large echo-free space anterior to the valve (white arrow) consistent with dehiscence. The dehiscence involves >50% of the sewing ring anteriorly. There are mobile echoes attached to the exterior of the anterior sewing ring, concerning for vegetation (yellow arrow). When color Doppler is added, a severe paravalvular leak is evident (**b**). Apical 4 chamber view demonstrates dehiscence (**c**, arrow) with severe paravalvular leak (**d**). *Key Findings: Prosthetic Valve present. Dehiscence. Perivalvular regurgitation. Aortic valve vegetation*

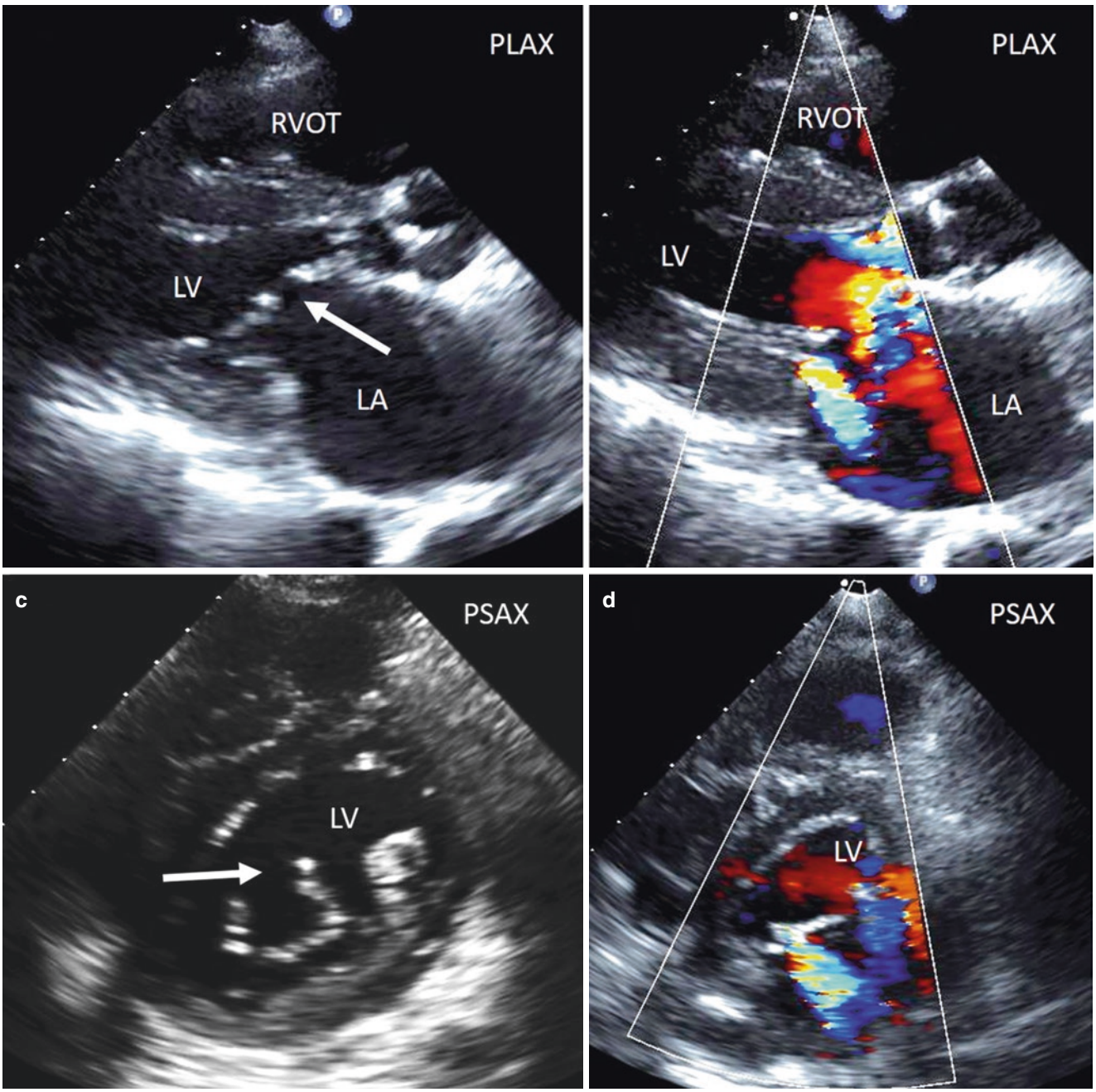


FIGURE 29-30

A 53-year-old woman with ASD repair at age 16 presents with atrial fibrillation. Mitral Valve Cleft. 2D TTE. PLAX shows anterior mitral valve cleft (**a**, arrow) with associated mitral regurgitation (**b**). PSAX views also demonstrate anterior MV cleft (**c**, arrow) and MR (**d**). *Key Findings: Mitral valve cleft. Moderate mitral regurgitation. Enlarged left atrium*

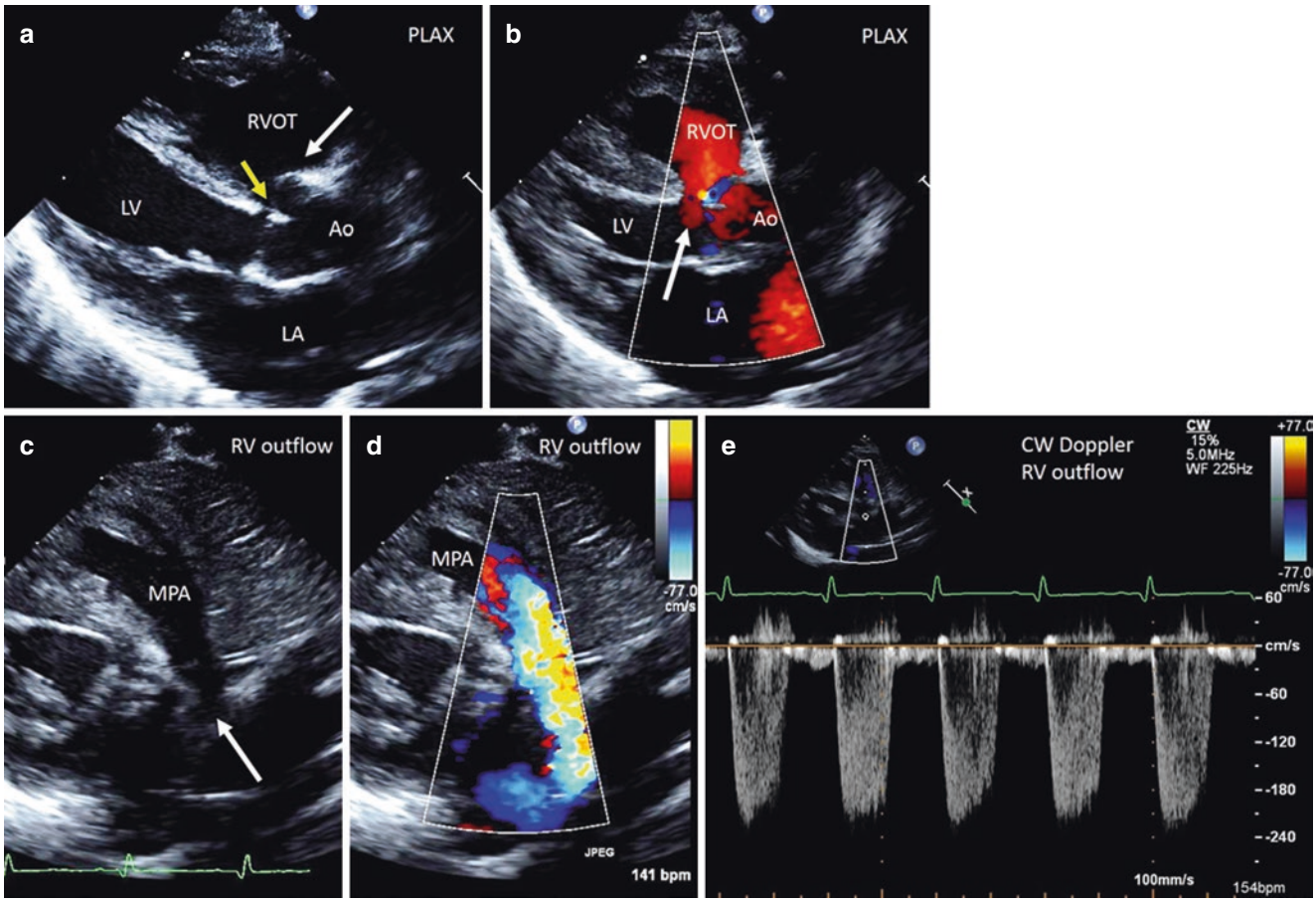


FIGURE 29-31

A 30-year-old woman with a history of multiple heart surgeries from birth. Tetralogy of Fallot. 2D TTE. PLAX view (**a**) showing overriding or anteriorly displaced aorta (white arrow) and subaortic VSD (arrow). Color Doppler of PLAX view (**b**) shows flow through the VSD. RV outflow view demonstrates pulmonic stenosis (**c**) confirmed by Color Doppler (**d**) and PW Doppler (**e**). RV hypertrophy is also evidence in panels (**a**–**c**). *Key Findings: Tetralogy of Fallot. Membranous VSD. Congenitally abnormal pulmonic valve*

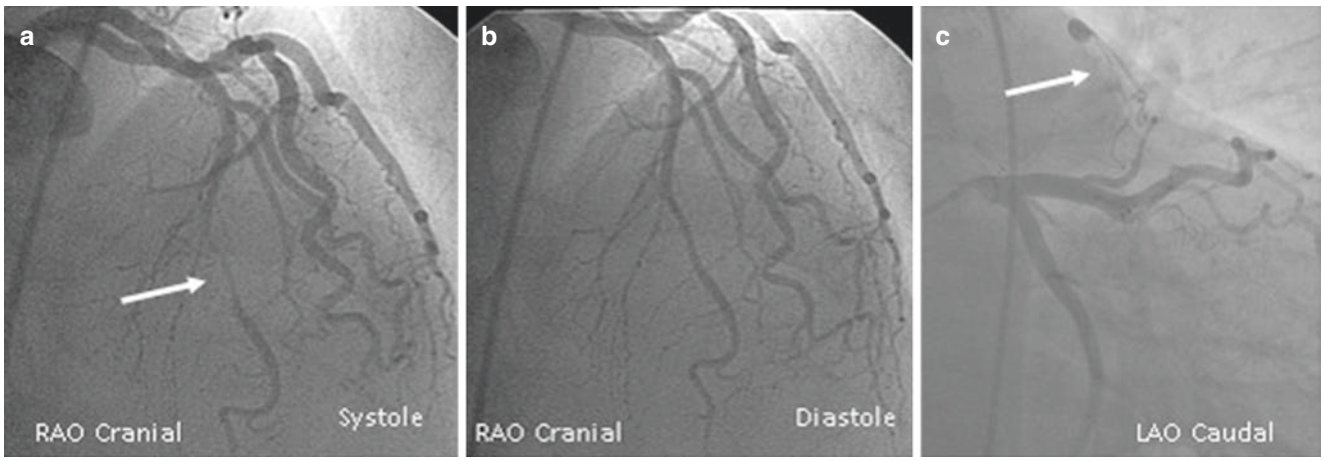


FIGURE 29-32

Coronary angiography of a patient with a myocardial bridge and a patient with a LAD to PA fistula. Panel (**a**) shows a RAO Cranial view in systole and diastole (**b**) of a patient with a myocardial bridge of the mid LAD (arrow). LAO Caudal view (**c**) of a patient with a LAD to PA fistula. *Key Findings: LAD myocardial bridge. LAD coronary fistula*

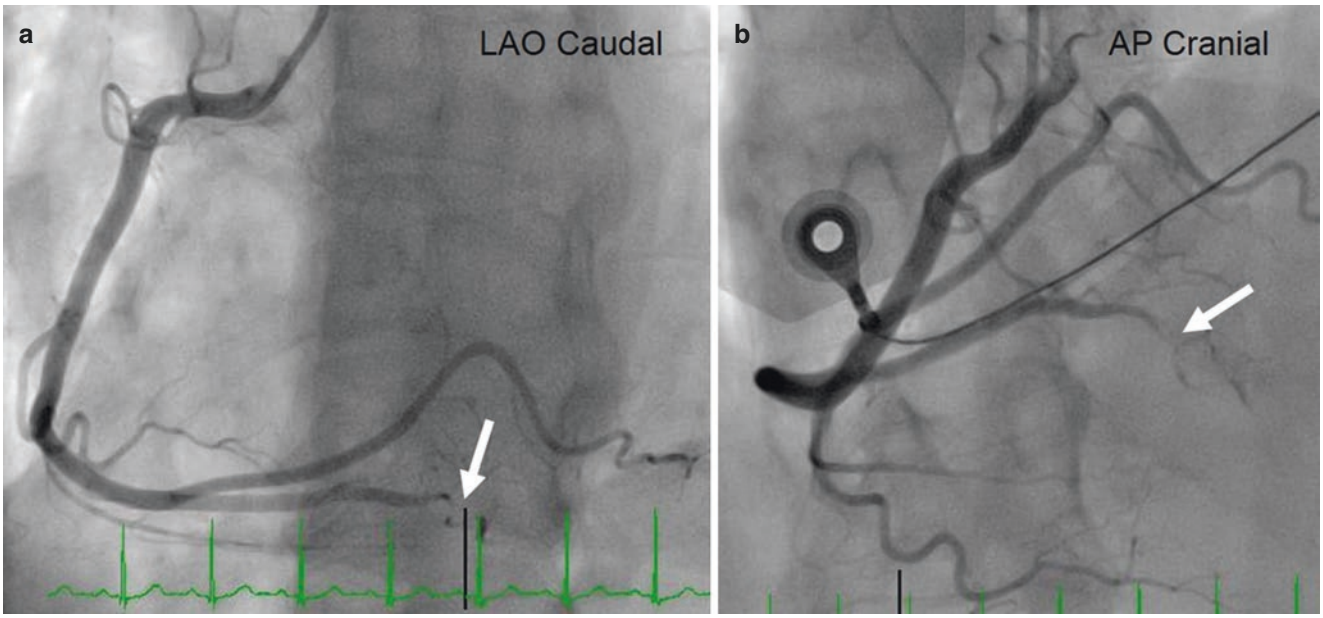


FIGURE 29-33

Coronary angiography of a patient with a spontaneous coronary artery dissection of the PDA. Panel (**a**) shows a LAO Caudal view and panel (**b**) shows an AP Cranial view of the dissection. *Key Findings: PDA dissection*

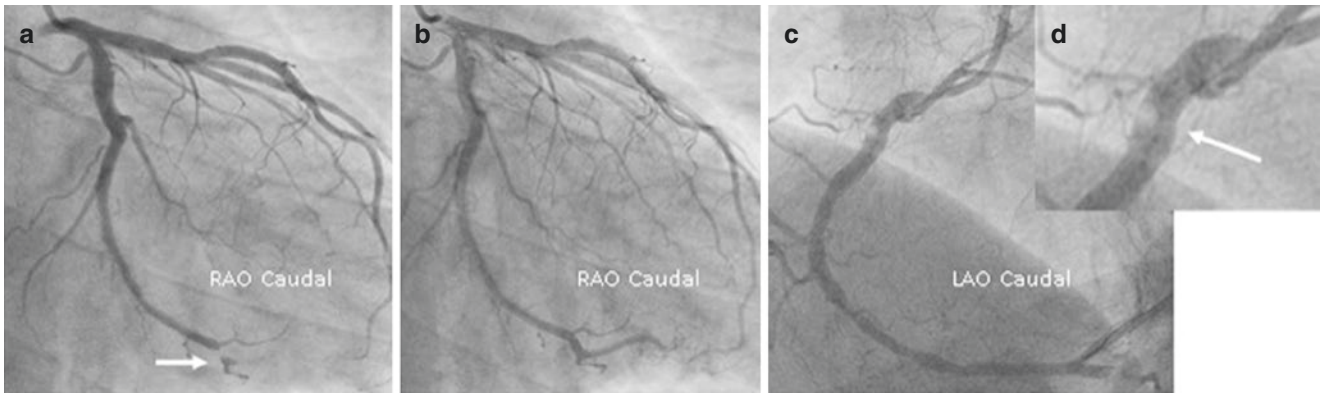


FIGURE 29-34

Coronary angiography of a patient with coronary vasospasm and of a patient with an air embolism. RAO Caudal view (**a**) showing obstruction to coronary flow distal in the LCx (arrow) which improves after administration of intracoronary nitroglycerine (**b**). Panel (**c**) is a LAO Caudal view of the RCA containing an air embolism (arrow) which is seen in close-up in panel (**d**). *Key Findings: LCx spasm*

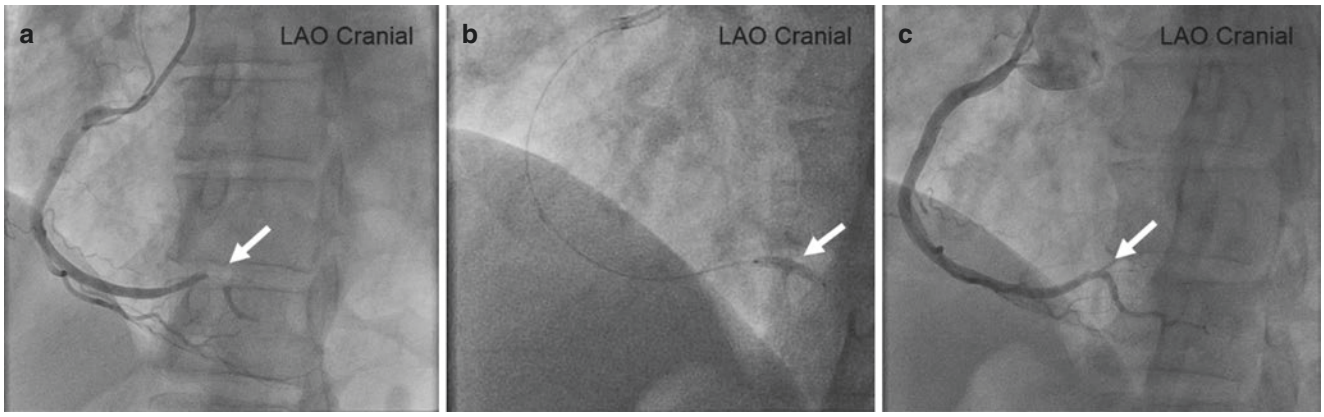


FIGURE 29-35

Coronary angiography of a patient with a known LV thrombus and found to have an RCA embolism. LAO Cranial view (**a**) showing obstruction to coronary flow distal in the RCA (arrow). Panel (**b**) shows plain old balloon angioplasty (POBA) of the RCA lesion (arrow) and panel (**c**) demonstrates the final angiographic result (arrow). *Key Findings: RCA total occlusion. RCA thrombus*

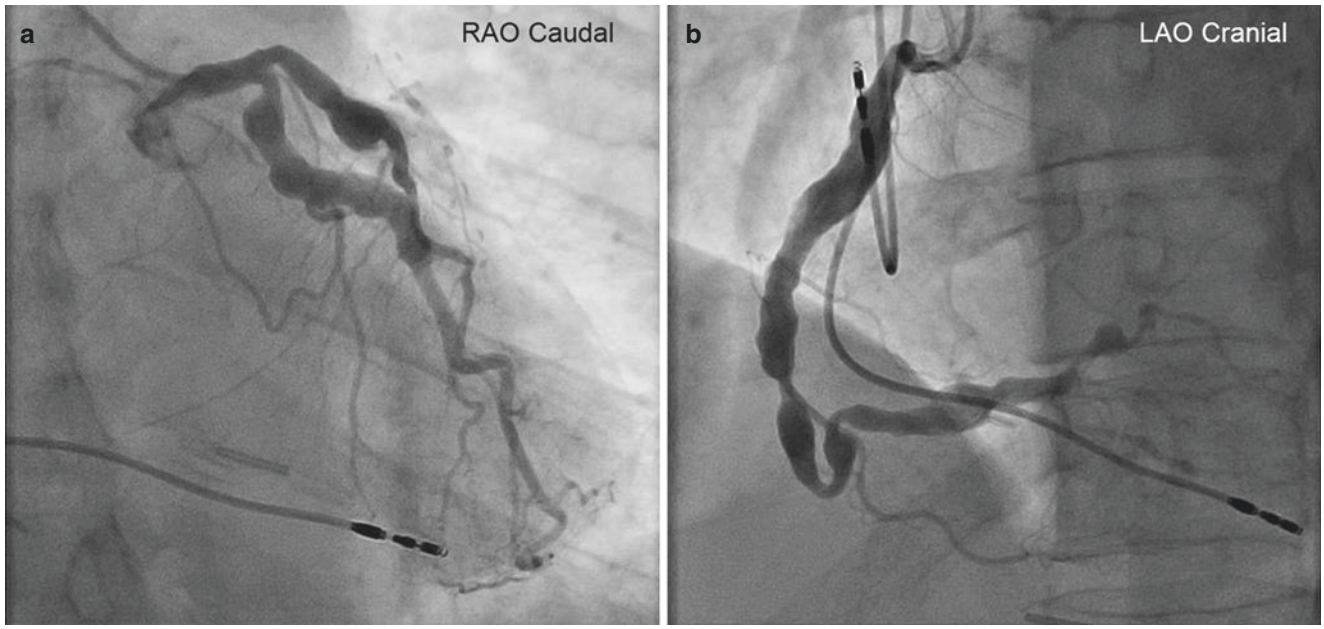


FIGURE 29-36

Coronary angiography of a patient with giant coronary aneurysms. RAO Caudal (**a**) view demonstrates multiple aneurysmal segments of the LAD and LCx. LAO Cranial (**b**) view demonstrates giant coronary aneurysms in the RCA. *Key Findings: LAD, LCx, and RCA aneurysm/severe ectasia*

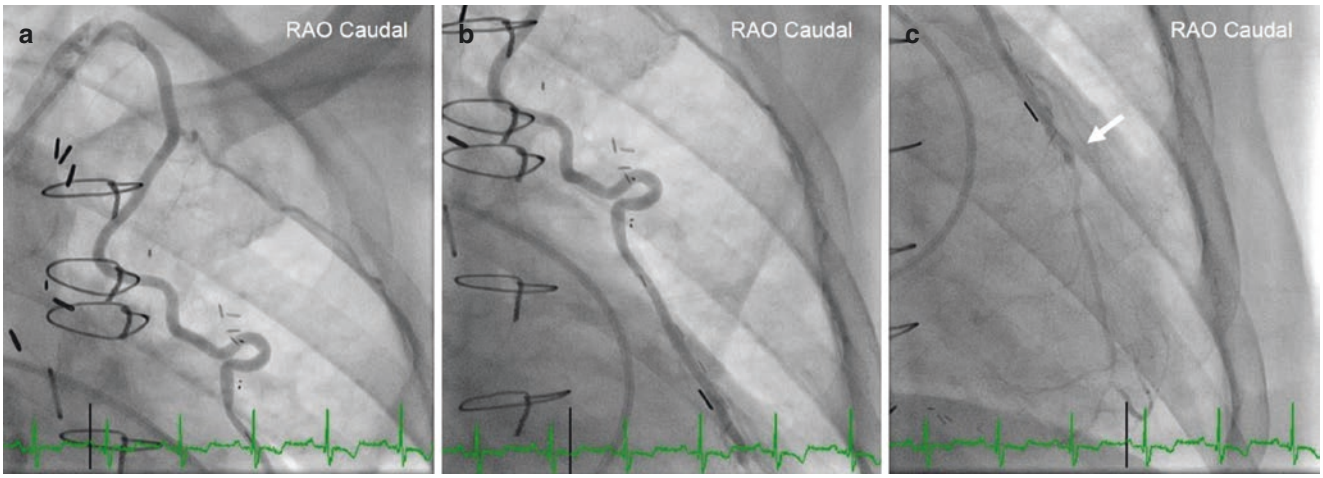


FIGURE 29-37

Coronary angiography of a patient with a patent left interior mammary artery (LIMA) to LAD bypass graft. RAO Caudal views of initial takeoff of LIMA (**a**), mid-course (**b**), and at anastomosis to native LAD (**c**, arrow). Panel (**c**) shows a heavily diseased native LAD. *Key Findings: Bypass graft to LAD*

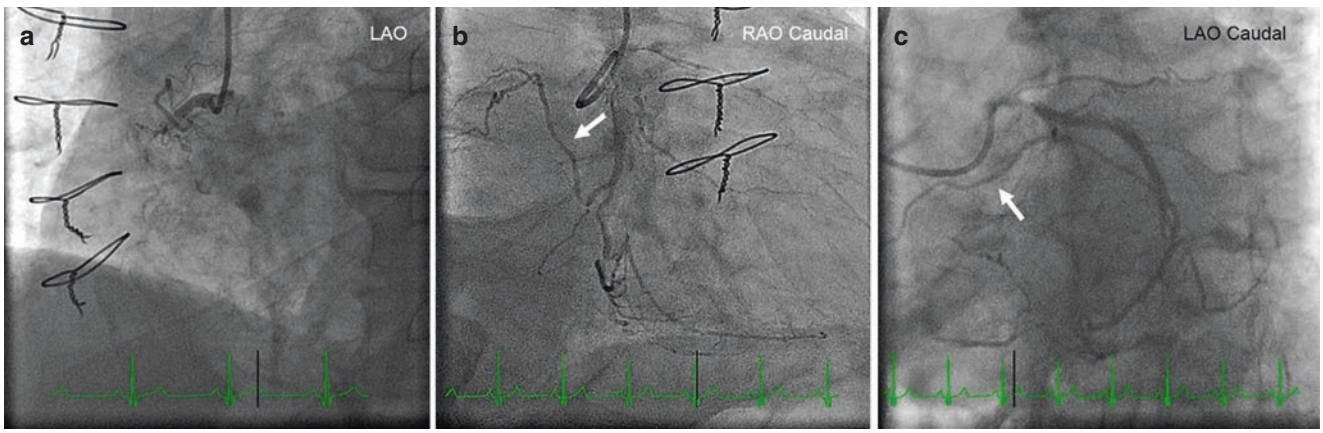


FIGURE 29-38

Coronary angiography of a patient with a complete total occlusion of the RCA (**a**) with left to right collaterals from the LCx (**b**, **c**). *Key Findings: RCA Total occlusion. RCA filled by collaterals*

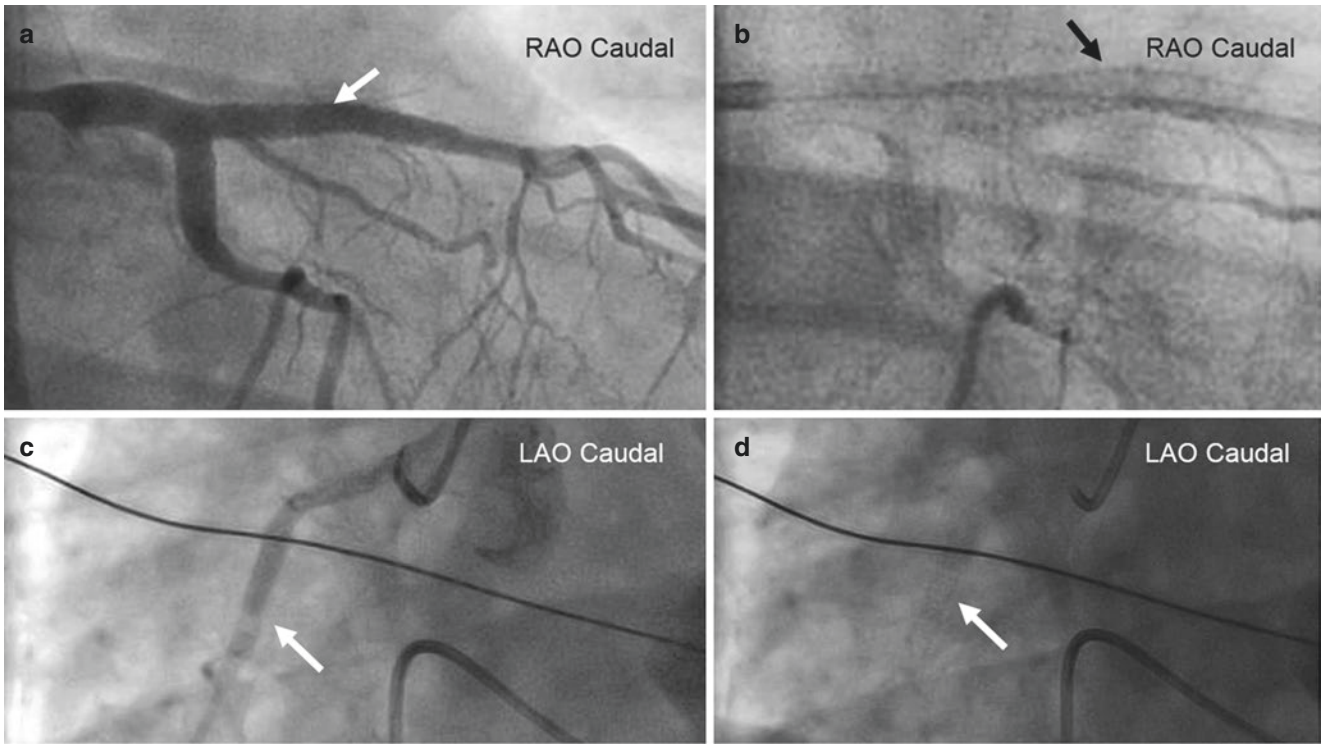


FIGURE 29-39

Coronary angiography of two patients with prior stenting. Panels (**a**, **b**) show a RAO Caudal view of a LAD stent that is patent (arrow). Panel (**c**, **d**) show a LAO Caudal view of an RCA stent with evidence of in-stent thrombosis (arrow). The RCA stent is under-expanded. *Key Findings: LAD stent: patent. RCA stent: occluded*

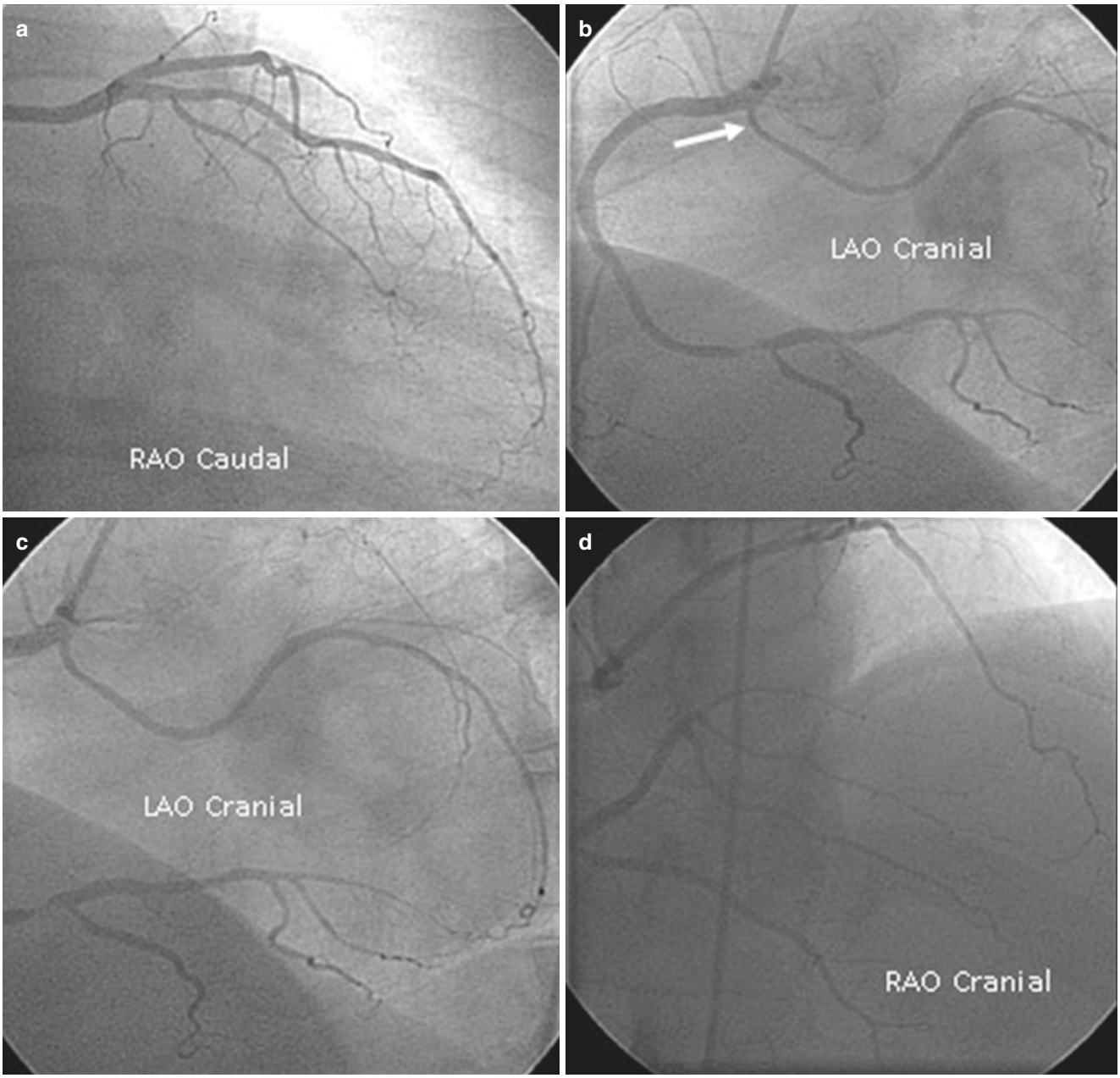


FIGURE 29-40

Coronary angiography of a patient with an anomalous LCx arising from the RCA. RAO Caudal (**a**) view of the left system showing the absence of the LCx. LAO Cranial (**b**) view of the RCA showing an anomalous vessel arising from the RCA and supplying the LCx territory (arrow). Panel (**c**) is a LAO Cranial view and panel (**d**) is an RAO Cranial view showing the full course of the anomalous LCx. Incidentally, a discrete 70% RCA stenosis is also visible mid-vessel. *Key Findings: LCx anomalous origin. RCA moderate stenosis*

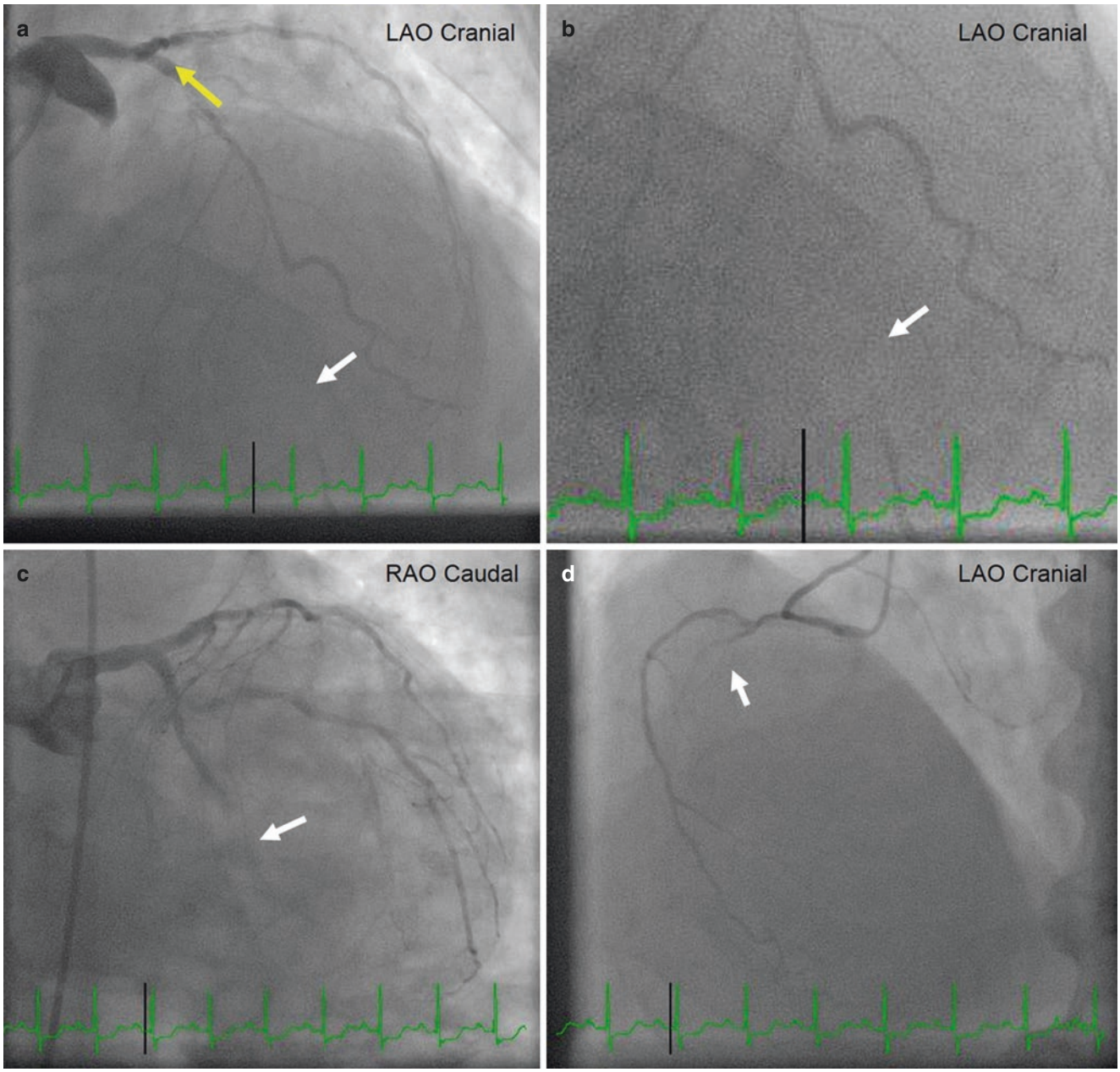


FIGURE 29-41

Coronary angiography of a patient with multivessel coronary artery disease. LAO Cranial view (**a**, **b**) of a severe stenosis of the proximal LAD (yellow arrow) and a long occlusion of the mid vessel at the second diagonal artery (white arrow). RAO Caudal view (**c**) demonstrates a mid-vessel thrombotic occlusion of the LCx after the first obtuse marginal artery (white arrow). LAO Cranial view (**d**) shows an occluded mid-RCA. *Key Findings: LAD severe stenosis. LAD, LCx, and RCA total occlusion*

CHAPTER 30

SAMUEL BERNARD, JORDAN LEYTON-MANGE, AND PHILIP PODRID

Electrocardiography

CHAPTER OUTLINE

ABBREVIATIONS

AIVR	Accelerated idioventricular rhythm
APB	Atrial premature beat
APC	Atrial premature complex
ASD	Atrial septal defect
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentrant tachycardia
AVRT	Atrioventricular reentrant tachycardia
CNS	Central nervous system
ECG	Electrocardiogram
IVCD	Intraventricular conduction delay
LA	Left atrium
LAFB	Left anterior fascicular block
LBBB	Left bundle branch block
LGL	Lown-Ganong-Levine
LPFB	Left posterior fascicular block
LV	Left ventricle
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
PAC	Premature atrial complex
PJB	Premature junctional beat
PJC	Premature junctional complex
PVB	Premature ventricular beat
PVC	Premature ventricular complex
RA	Right atrium
RBBB	Right bundle branch block
RV	Right ventricle
RVH	Right ventricular hypertrophy
STEMI	ST-elevation myocardial infarction
VA	Ventriculoatrial
VF	Ventricular fibrillation
VPB	Ventricular premature beat
VPC	Ventricular premature complex
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White

BASICS

A. **Normal electrocardiogram** (ECG) is shown in Fig. 30-1.

- **P wave**—Normal duration < 0.12 s (3 small boxes in width) and amplitude <2.5 mm (2.5 boxes in height). Normal P wave (from sinus node) is upright (positive) in leads I, II, aVF, V4–V6, negative in aVR and usually biphasic (positive-negative) in V1.
- **PR interval**—Interval measured from the beginning of the P wave (atrial depolarization) to the first wave of the QRS complex (conduction through atrioventricular [AV] node and His-Purkinje system). Normal duration is ≥0.12 and ≤0.20 s. PR segment changes with autonomic tone, shortening with sinus tachycardia and lengthening with sinus bradycardia (due to changes in AV nodal conduction velocity).
- **QRS complex**—Duration is measured from the beginning of QRS complex (Q or R wave) to the J point (end of QRS complex and beginning of ST segment). The normal duration is ≥0.06 and <0.10 s. The QRS complex does not change with normal physiologic rates. The normal QRS complex is positive in leads I, II, aVF, and V4–V6 and negative in aVR. Small septal Q waves are often seen in the limb and lateral precordial leads and small septal R waves may be seen in V1.
- **ST segment**—ST segment begins at the J point and ends at the onset of the T wave. The ST segment is slightly concave, but isoelectric (established by the T-P segment).
- **QT interval**—Interval measured from the beginning of the QRS complex (Q or R wave) to the end of the T wave. The QT interval changes with heart rate, shortening with tachycardia and lengthening with bradycardia.
  - The QT interval is corrected for rate (QTc) using Bazett's formula, where QTc = QT interval (in milliseconds) divided by the square root of the *preceding* RR interval (in seconds). Normal QTc < 0.48 s.
  - As the QT interval includes the QRS complex, the former needs to be corrected for an increased QRS duration. First, the QRS duration is measured. Subsequently, the number of milliseconds beyond 100 ms (the normal QRS duration) is subtracted from the measured QT interval. This adjusted QT interval can then be used in Bazett's formula.

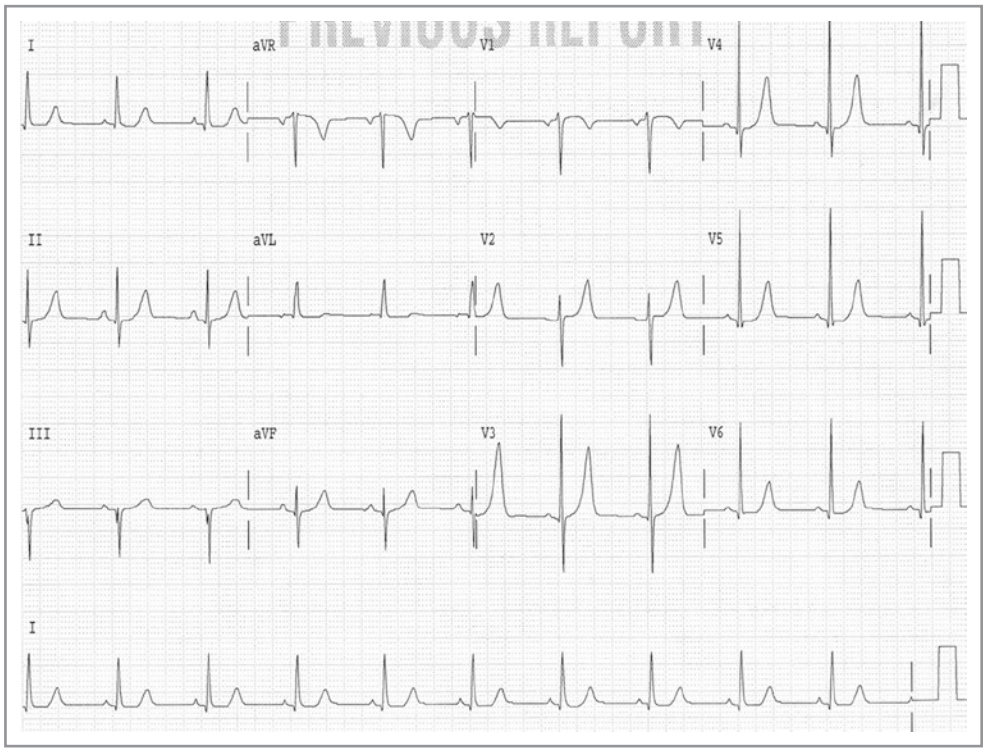


FIGURE 30-1

Normal ECG. Even if you have the correct diagnosis, do not forget to code the underlying rhythm such as *sinus rhythm*

- **T wave**—T wave is smooth, but asymmetric (regardless of amplitude) with a slower upstroke than downstroke. The T wave axis is typically the same as that of the QRS complex.
- **U wave**—Follows the T wave, but is **not included** in the QT interval measurement. Normally a low amplitude waveform seen in the right precordial leads (V1–V3) with an upright axis.

B. **QRS axis in frontal plane**

- **Normal axis** (0° to +90°)—QRS positive in leads I, II, aVF.
- **Physiologic left axis** (0° to −30°)—QRS positive in leads I, II and negative in lead aVF.
- **Pathologic left axis** (−30° to −90°)—QRS positive in lead I, and negative in leads II and aVF. This is known as a **left anterior fascicular block** (LAFB; Fig. 30-2a) when no other reason for left axis deviation exists (i.e. prior inferior MI with Qr complex in leads II, III and aVF).
- **Right axis** (≥+90°)—QRS negative in lead I and positive in lead aVF. This is known as a **left posterior fascicular block** (LPFB; Fig. 30-2b) when no other reason for right axis deviation exists:
  - Lateral MI (Qr in leads I and aVL)
  - Right-left arm lead reversal (P, QRS and T waves are negative in leads I and aVL, but positive in lead aVR)
  - Dextrocardia (see "Dextrocardia")
  - WPW (see "Wolff-Parkinson-White")
  - RVH

C. **QRS complex**

- QRS ≥ 0.10 s is called an intraventricular conduction delay (IVCD, see "Intraventricular conduction delay"). If ≥0.12 s, may be a bundle branch block (see

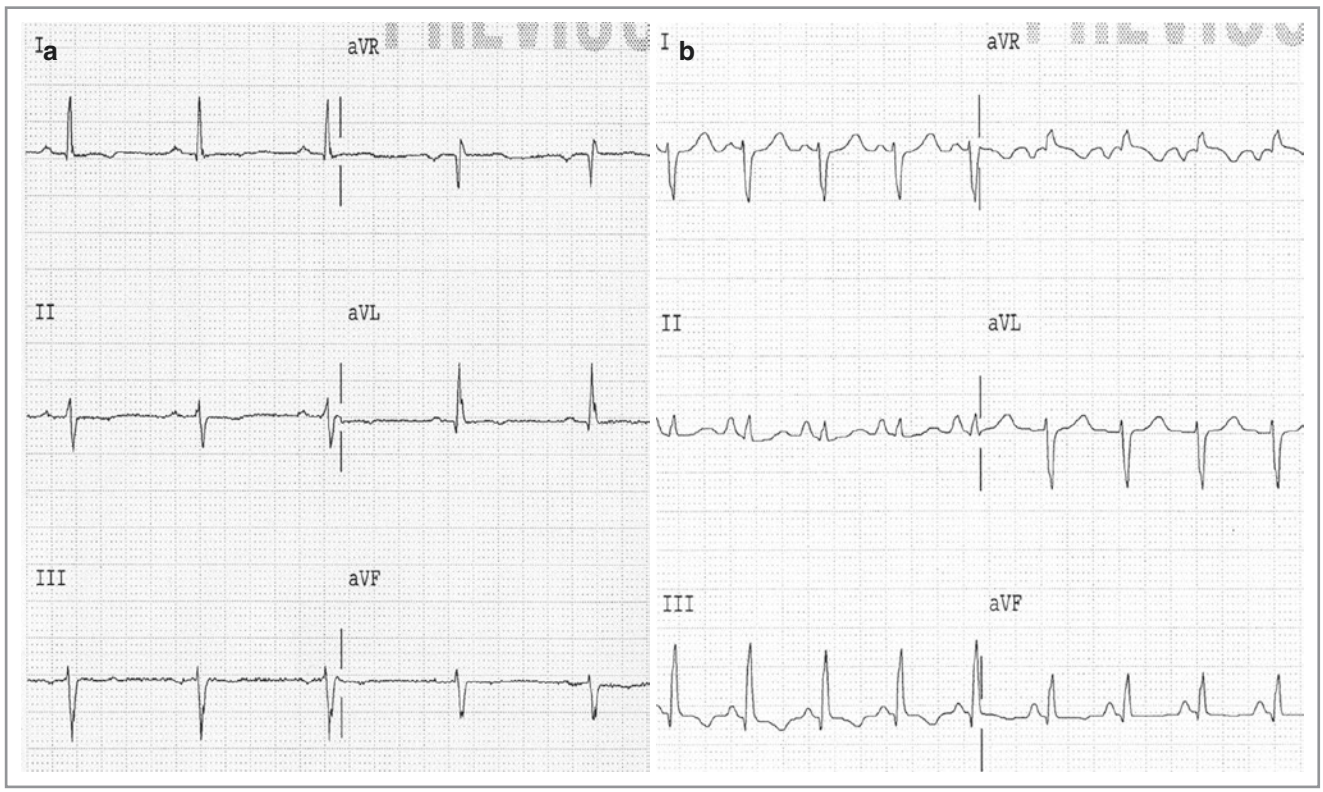
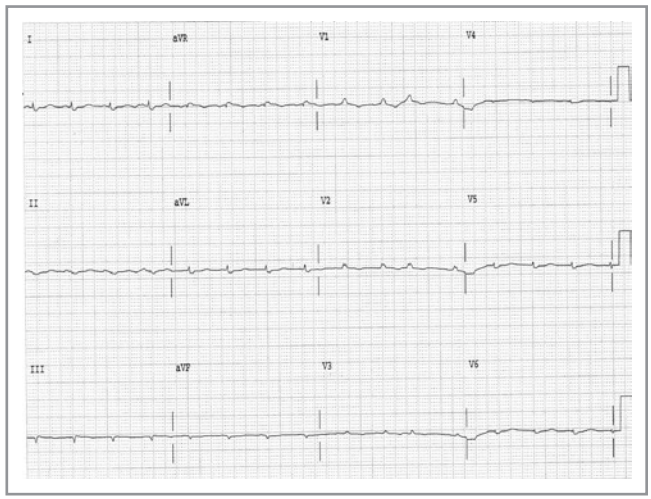


FIGURE 30-2

(**a**) *Left anterior fascicular block*; (**b**) *left posterior fascicular block*

FIGURE 30-3

Low voltage. Make sure to specify *limb leads* or *precordial leads.* Note the standardization indicator on the right



"Right bundle branch block" and "Left bundle branch block"). Nonspecific QRS complex widening >0.18 and <0.22 s is seen with dilated cardiomyopathy, and when ≥0.24 s is pathognomonic for hyperkalemia.

- QRS complex duration may also be prolonged if there is pre-excitation (e.g.WPW), rate related aberration or Ashman's phenomenon (see "Aberration").
- Low QRS voltage is defined as QRS amplitude <5 mm in each limb lead and/or <10 mm in each precordial lead. It reflects reduced electrical activity recorded at the surface of the body (Fig. 30-3).

D. **QT interval**

- Prolonged QT interval, QTc generally > 0.50 msec (Fig. 30-4) may be due to:
  - **Delayed repolarization**—The ST segment is long while the T wave duration is normal. Seen with metabolic abnormalities, particularly hypocalcemia or hypomagnesemia (see "Hypocalcemia").
  - **Prolonged repolarization**—The ST segment is normal in duration, but the T wave is broad. This is due to drugs (acquired QT prolongation) or a genetic abnormality producing a channelopathy (congenital long QT syndrome, especially types I and II). Congenital QT prolongation may have a prominent U wave on top of or interrupting the T wave (QT-U wave).
- Short QT interval QTc generally <340 msec (Fig. 30-4d) is due to a metabolic abnormality (hypercalcemia or hypermagnesemia, see "Hypercalcemia") or a congenital short QT syndrome.
- U waves should note be included in the QT interval measurement.

E. **T waves**

- Normal T waves are **asymmetric** (upstroke slower than downstroke) and smooth in upstroke and downstroke.
- Young patients may have T wave inversions in leads V1–V3, which are normal and are termed juvenile T waves (Fig. 30-5).
- Tall, peaked and **symmetric** T waves (termed hyperacute T waves; Fig. 30-6) may be seen with acute MI or hyperkalemia (see "Acute MI" and "Hyperkalemia").
- Deeply inverted asymmetric T waves (upstroke slower than downstroke) with a prolonged QT interval due to broad T wave (termed cerebral T waves; Fig. 30-7) may be seen with a central nervous system (CNS) disorder such as subarachnoid hemorrhage, mass lesion, or hepatic or metabolic encephalopathy.
- Other T wave abnormalities (e.g. flattened, biphasic or inverted) are non-specific and may be seen in a variety of other clinical contexts.

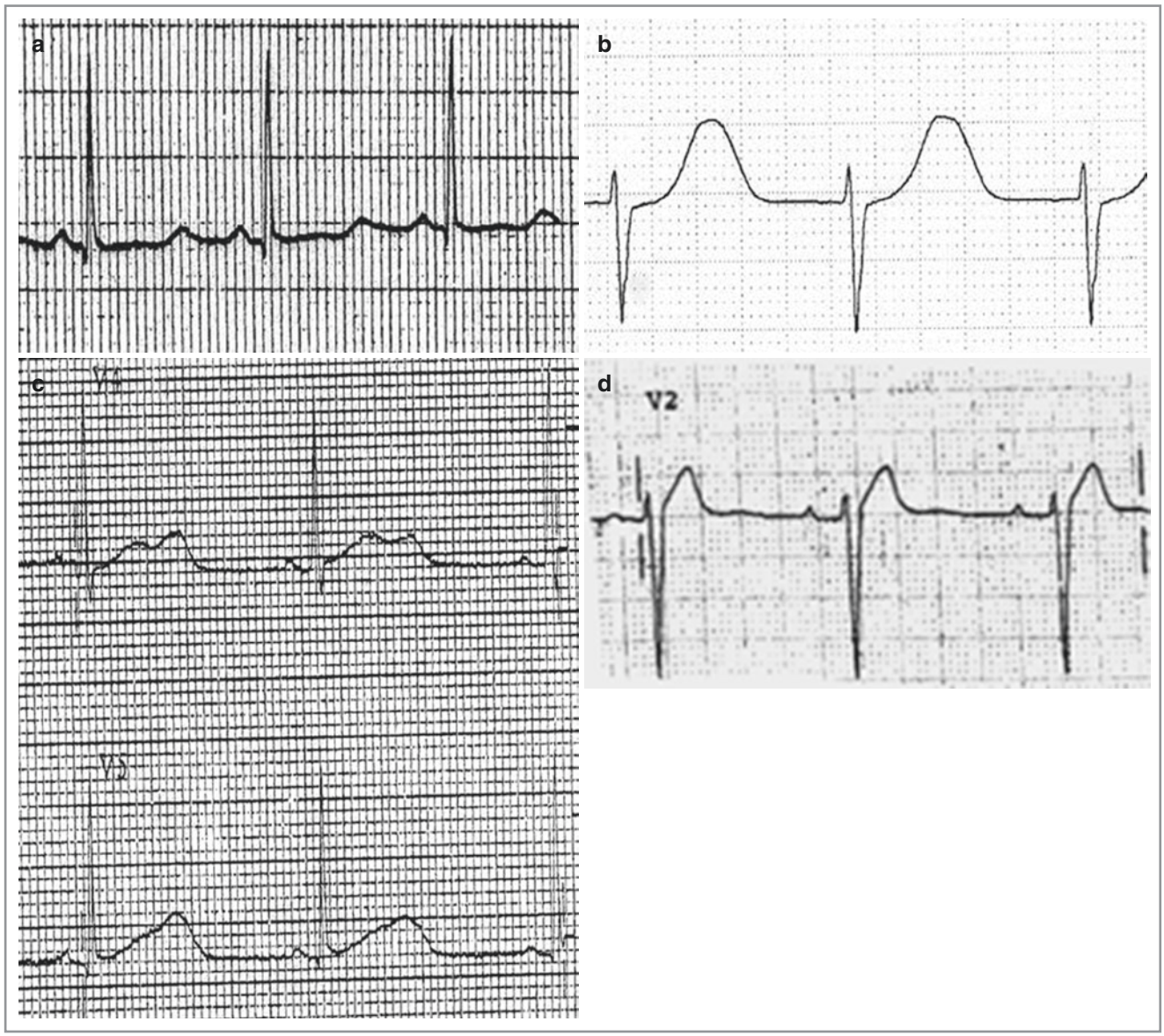


FIGURE 30-4

(**a**) *Prolonged Q-T interval* with long ST segment (*ST and/or T wave abnormalities suggesting electrolyte disturbances*) due to delayed repolarization as seen with *hypocalcemia*; (**b**) *prolonged Q-T interval* from prolonged repolarization, as seen with medications; (**c**) *prolonged Q-T interval* due to congenital long QT with QT-U waves; (**d**) short QT interval (*ST and/or T wave abnormalities suggesting electrolyte disturbances*), as may be seen in *hypercalcemia*

F. **U waves**

- Represent late repolarization of the His-Purkinje system or papillary muscles.
- Normally observed in leads V1–V3, are in the same direction as the T wave, and are <2 mm in amplitude.
- U waves may be more prominent in bradyarrhythmias, hypokalemia, hypothermia, LVH, CAD and with antiarrhythmic drugs (including class IA, class III, and digoxin).

G. **ST segment changes**

- J point and ST segment elevation
  - Seen in transmural ischemia (i.e. STEMI, see "Myocardial infarction"), pericarditis, ventricular aneurysm (with an old MI), and early repolarization (normal or with left ventricular hypertrophy [LVH]).

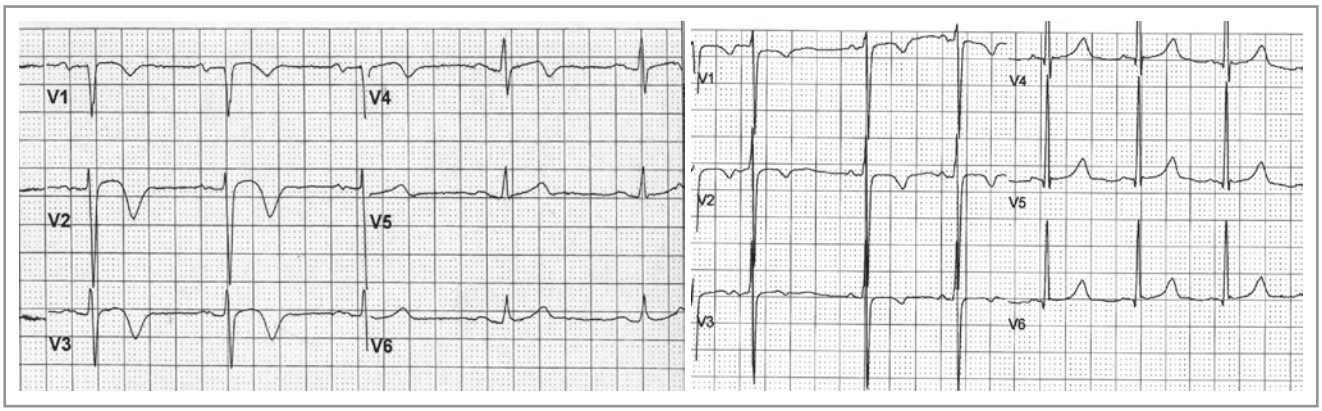


FIGURE 30-5

Normal variant, juvenile T waves. Two examples of juvenile T wave patterns with T wave inversions in leads V1–V3

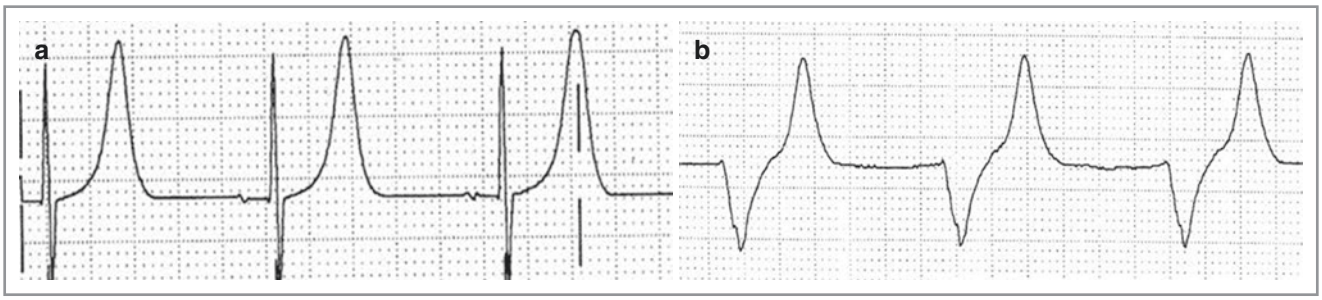
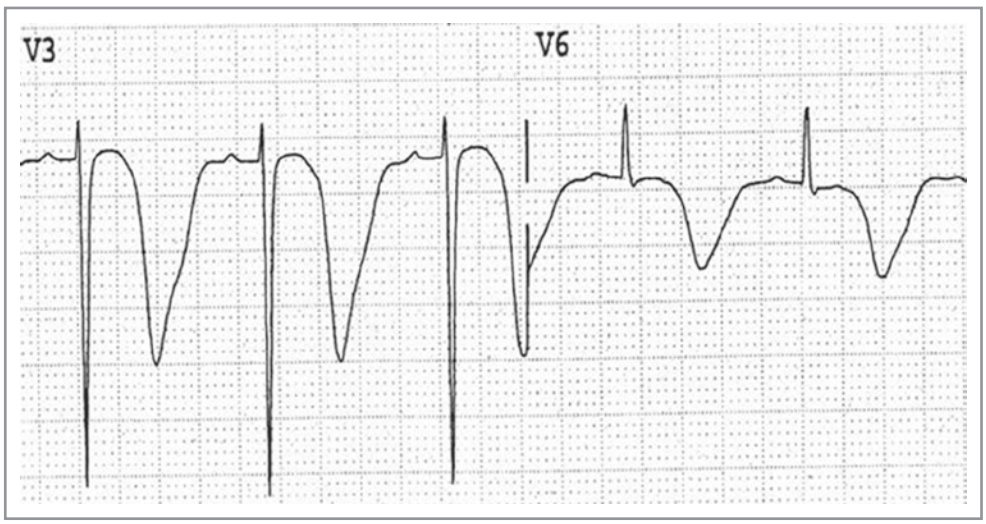


FIGURE 30-6

Tall, peaked and **symmetric** T waves seen in the setting of (**a**) acute myocardial infarction and (**b**) *hyperkalemia* (*ST and/or T wave abnormalities suggesting electrolyte disturbances*). Note the concomitant prolonged QRS in the latter

FIGURE 30-7

Deeply inverted, asymmetric and broad T waves from an acute *central nervous system disorder*, a subarachnoid bleed in this case



- J point and ST depression
  - Upsloping may be seen with tachycardia due to atrial repolarization, wherein atrial T waves alter the J point (i.e. "TA" waves, Fig. 30-8a). If upsloping ST depression still >1.5 mm below baseline at 80 msec past J point this is possibly ischemia.
  - Horizontal or downsloping (>1 mm below baseline) due to subendocardial ischemia (e.g. LVH or coronary disease; Fig. 30-8b, c).

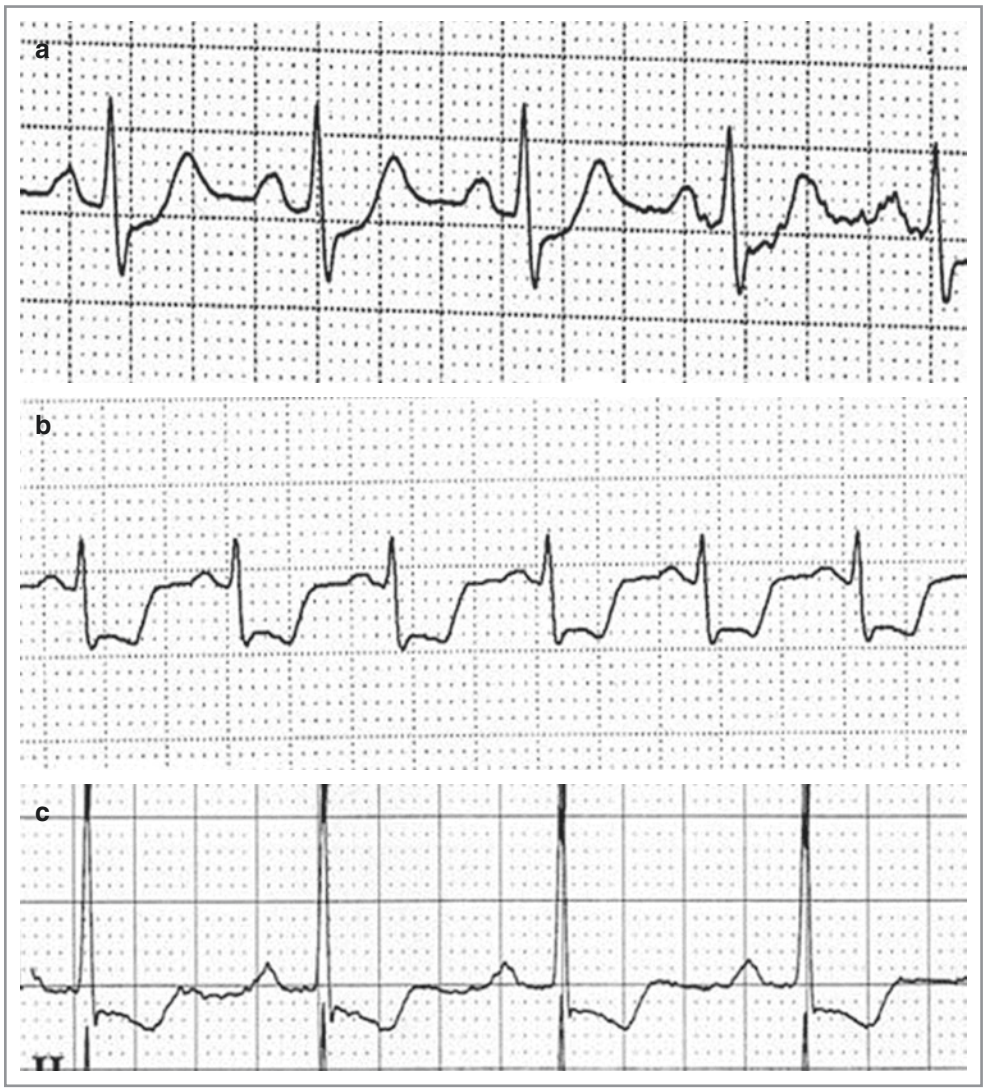


FIGURE 30-8

(**a**) Upsloping ST depressions which may be seen in the setting of *sinus tachycardia* due to atrial repolarization (*nonspecific ST and/or T wave abnormalities*); (**b**) horizontal and (**c**) downsloping ST depressions due to subendocardial ischemia (*ST and/or T wave abnormalities suggesting myocardial ischemia*)

PACEMAKERS (FIGS. 30-9 AND 30-10)

- Single chamber (RA or RV), dual chamber (RA and RV) or biventricular (LV and RV) pacemaker.
- **RV pacing**—QRS complex has LBBB morphology (broad R wave in leads I, V5, V6 and QS in lead V1).
- **Biventricular (CRT) pacing**—RBBB morphology in lead V1 combined with a Q wave or QS complex in lead I (and often V5 and V6).
- Fixed rate (asynchronous) or demand mode.
- Mode of pacing may be atrial pacing, ventricular pacing, P wave synchronous ventricular pacing, or AV sequential pacing.
- Failure of pacemaker sensing generally results in over pacing (atrial and/or ventricular stimuli despite P wave or QRS complex). Failure of myocardial capture is represented by pacemaker spikes with the absence of myocardial depolarization (P wave or QRS complex; Fig. 30-11).

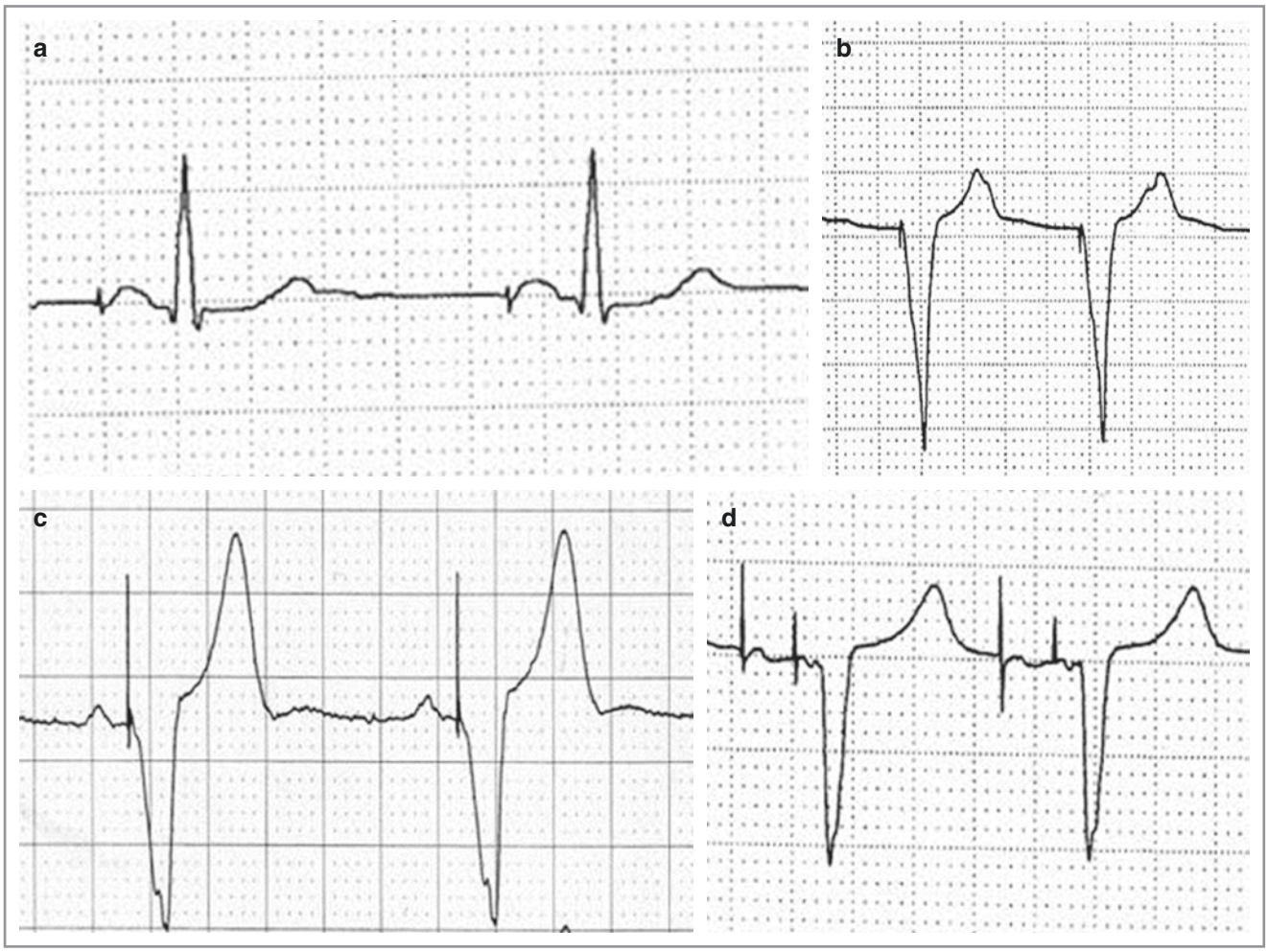


FIGURE 30-9

(**a**) Atrial pacing (*atrial or coronary sinus pacing*); (**b**) ventricular pacing (*ventricular demand pacemaker (VVI), normally functioning*); (**c**) P wave synchronous ventricular pacing (*ventricular demand pacemaker (VVI), normally functioning*); (**d**) A-V sequential pacing (dual-chamber pacemaker (DDD), normally functioning). ∗Remember to also code the underlying rhythm, regardless of pacemaker status

HYPERTROPHY

A. **Left atrial abnormality/hypertrophy** (Fig. 30-12)

- Also referred to as left atrial enlargement.
- P wave is ≥0.12 s with prominent notching in lead II ("P mitrale") or terminal negative portion of P wave ≥1 mm and ≥0.04 s in lead V1.

B. **Right atrial abnormality/hypertrophy** (Fig. 30-13)

- Also referred to as right atrial enlargement.
- P wave narrow and peaked with amplitude >2.5 mm in lead II ("P pulmonale") or P wave positively deflected ≥1 mm and ≥0.04 s in lead V1.
- Right and left atrial abnormality/hypertrophy may coexist in the same patient (i.e. biatrial abnormality/hypertrophy).

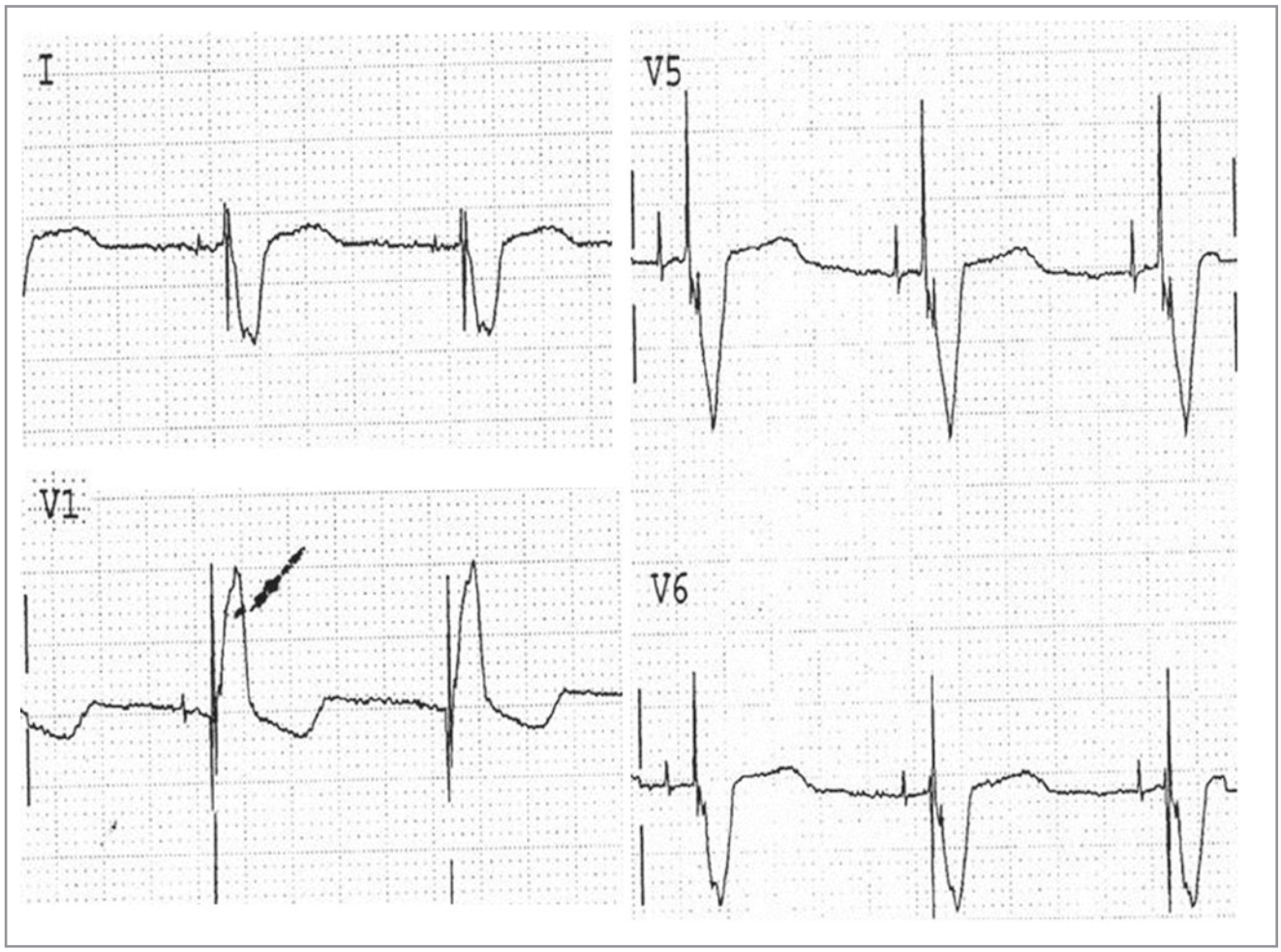


FIGURE 30-10

Biventricular pacing (*paced morphology consistent with biventricular pacing or cardiac resynchronization therapy*)

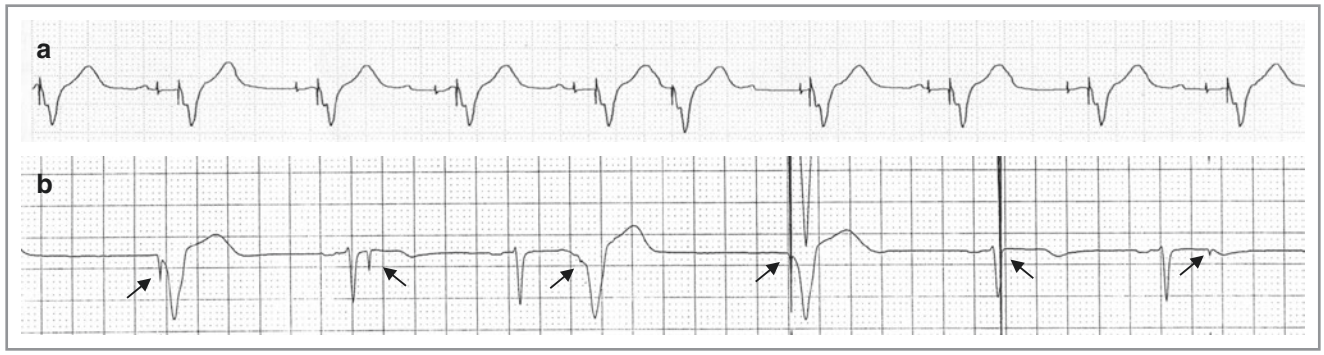


FIGURE 30-11

(**a**) Failure of atrial sensing and atrial capture; (**b**) failure of ventricular sensing with intermittent capture (arrows denote ventricular pacing spikes). Both *pacemaker malfunction, not constantly capturing (atrium or ventricle)* and *pacemaker malfunction not constantly sensing (atrium or ventricle)* should be coded here

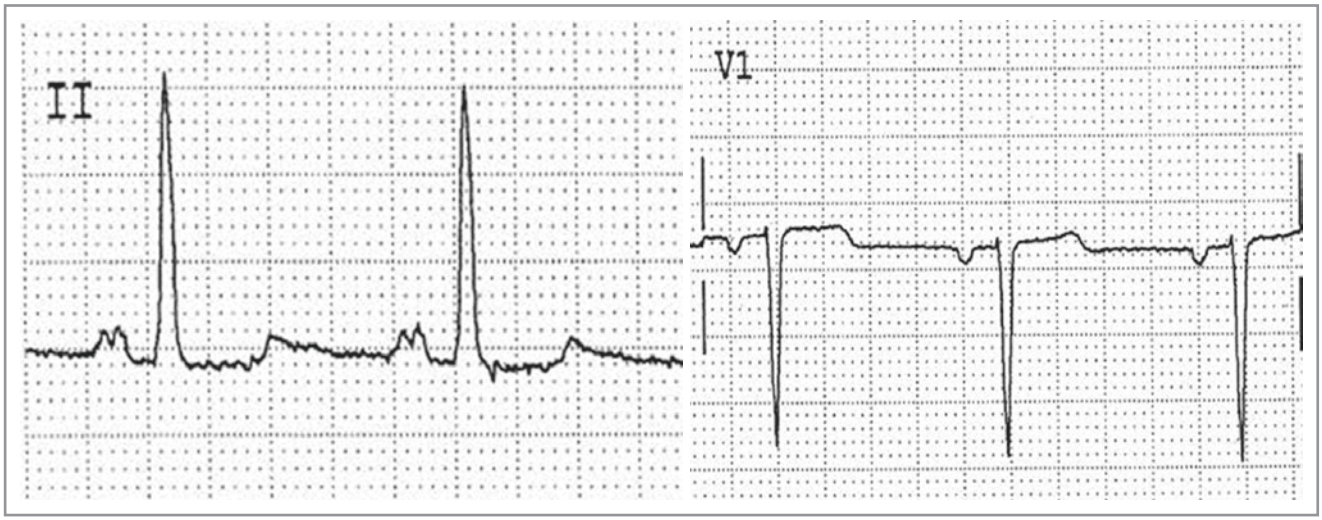


FIGURE 30-12

Left atrial abnormality/enlargement

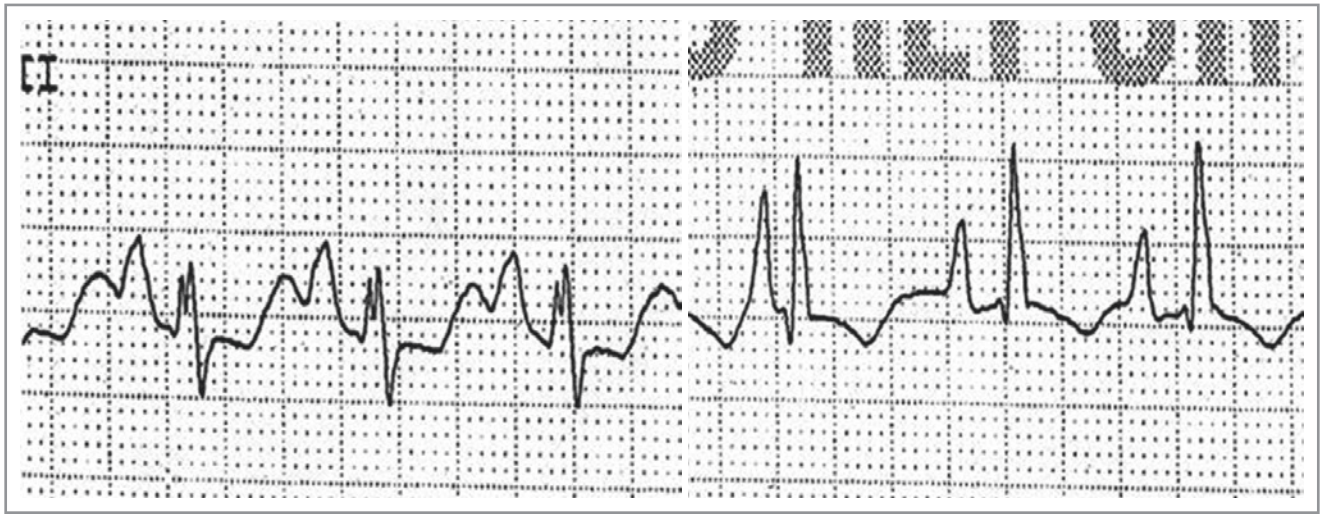


FIGURE 30-13

Right atrial abnormality/hypertrophy/enlargement

C. **Left ventricular hypertrophy** (Fig. 30-14)

- Sokolow-Lyon
  - S wave in V1 or V2 + R wave in V5 or V6 ≥35 mm if over age 45, ≥45 mm if under age 45
  - R wave in aVL ≥ 11 mm (≥18 mm in presence of left axis deviation)
  - S wave depth or R wave amplitude in any one precordial lead ≥25 mm
  - R wave ≥20 mm in any limb lead
- Cornell
  - S wave in V3 + R wave in aVL > 28 mm (men) and >20 m (women)

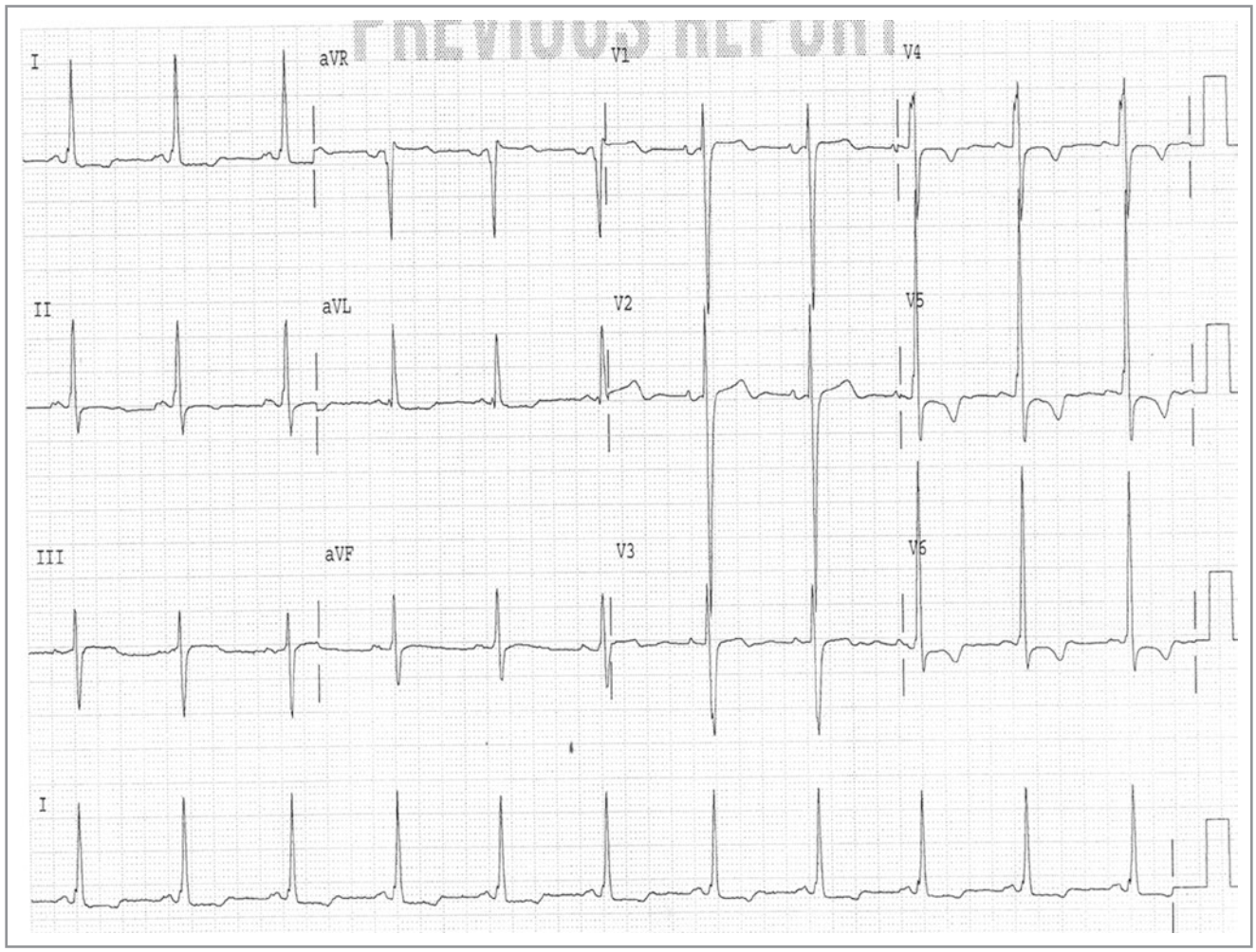


FIGURE 30-14

Left ventricular hypertrophy with repolarization abnormalities (*ST and/or T wave abnormalities secondary to hypertrophy*)

- Romhilt-Estes scoring system (5 points = definite LVH, 4 points = probable LVH)
  - R or S wave in any limb lead ≥20 mm = 3 points
  - S wave in V1 or V2 ≥ 30 mm = 3 points
  - R wave in V5 or V6 ≥ 30 mm = 3 points
  - Left atrial abnormality/hypertrophy/enlargement (as determined by V1) = 3 points
  - Ischemic ST-T wave changes (opposite of QRS axis, also referred to as LV strain) *without* digitalis = 3 points
  - Ischemic ST-T wave changes (opposite of QRS axis, also referred to as LV strain) *with* digitalis = 1 point
  - Left axis deviation = 2 points
  - QRS duration ≥0.09 s = 1 point
  - Delayed intrinsicoid deflection (beginning of QRS complex to peak of R wave) ≥0.05 s) = 1 point

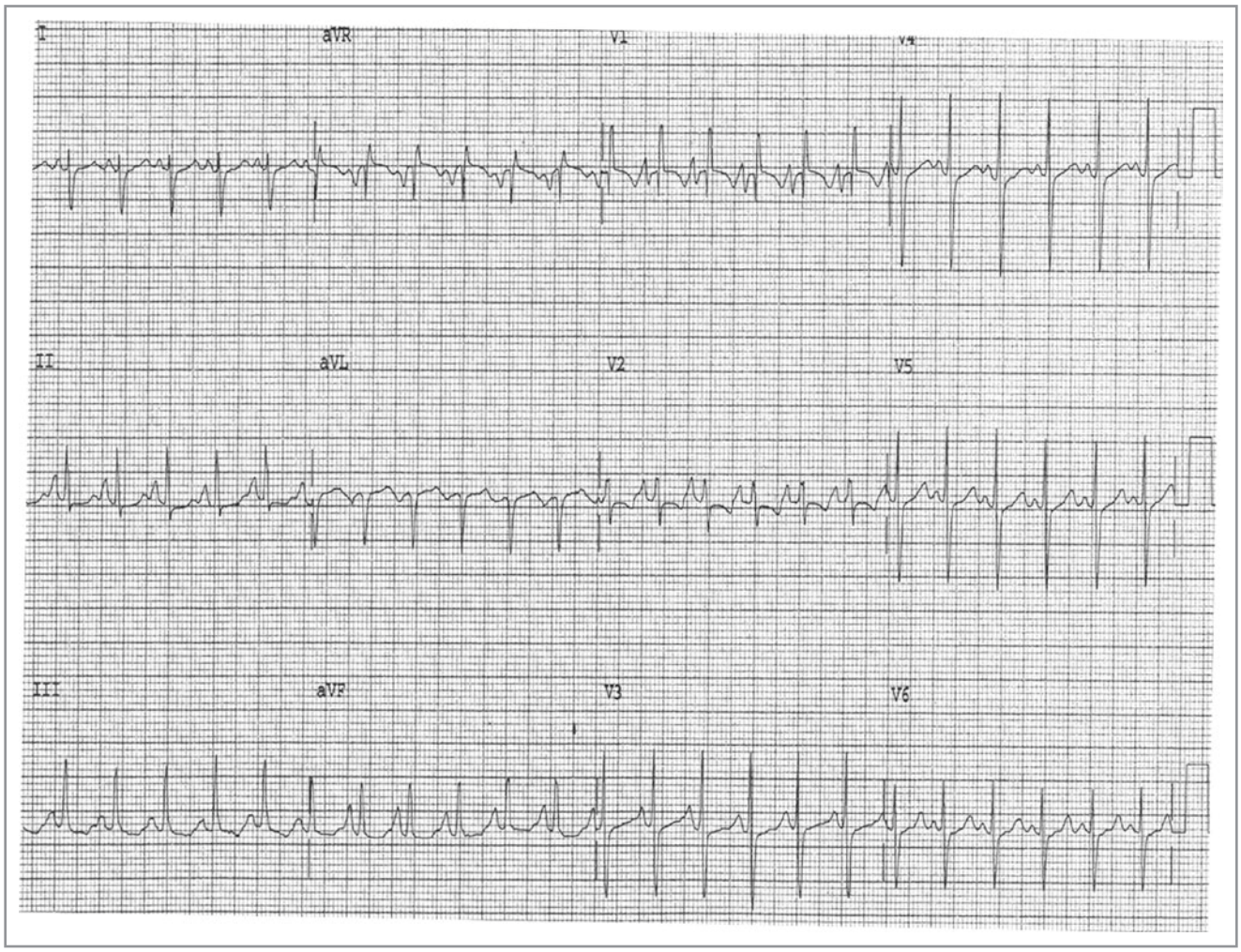


FIGURE 30-15

Right ventricular hypertrophy and *right atrial abnormality/hypertrophy/enlargement*

D. **Right ventricular hypertrophy** (Fig. 30-15)

- Features characteristic of RVH include the following:
  - R in V1 >7 mm
  - R/S ratio in V1 >1
  - R/S ratio in V6 <1
  - Right axis deviation
  - Right atrial abnormality ("P pulmonale")
  - Associated ST-T wave abnormalities in leads V1–V3
- Need to exclude other causes for tall R wave in V1, including
  - Posterior wall MI (often associated with inferior wall MI)
  - Hypertrophic cardiomyopathy (asymmetric septal hypertrophy)
  - Dextrocardia (right axis, negative P and T waves in leads I and avL and positive in lead avR and reverse R wave progression V1–V6)
  - WPW (short PR and delta wave)
  - Duchenne's or Becker's muscular dystrophy (also with lateral Q waves suggesting posterior lateral MI pattern)
  - Incorrect lead placement (V1–V3 lead switch)
- LVH and RVH may coexist on the same ECG (Fig. 30-16).

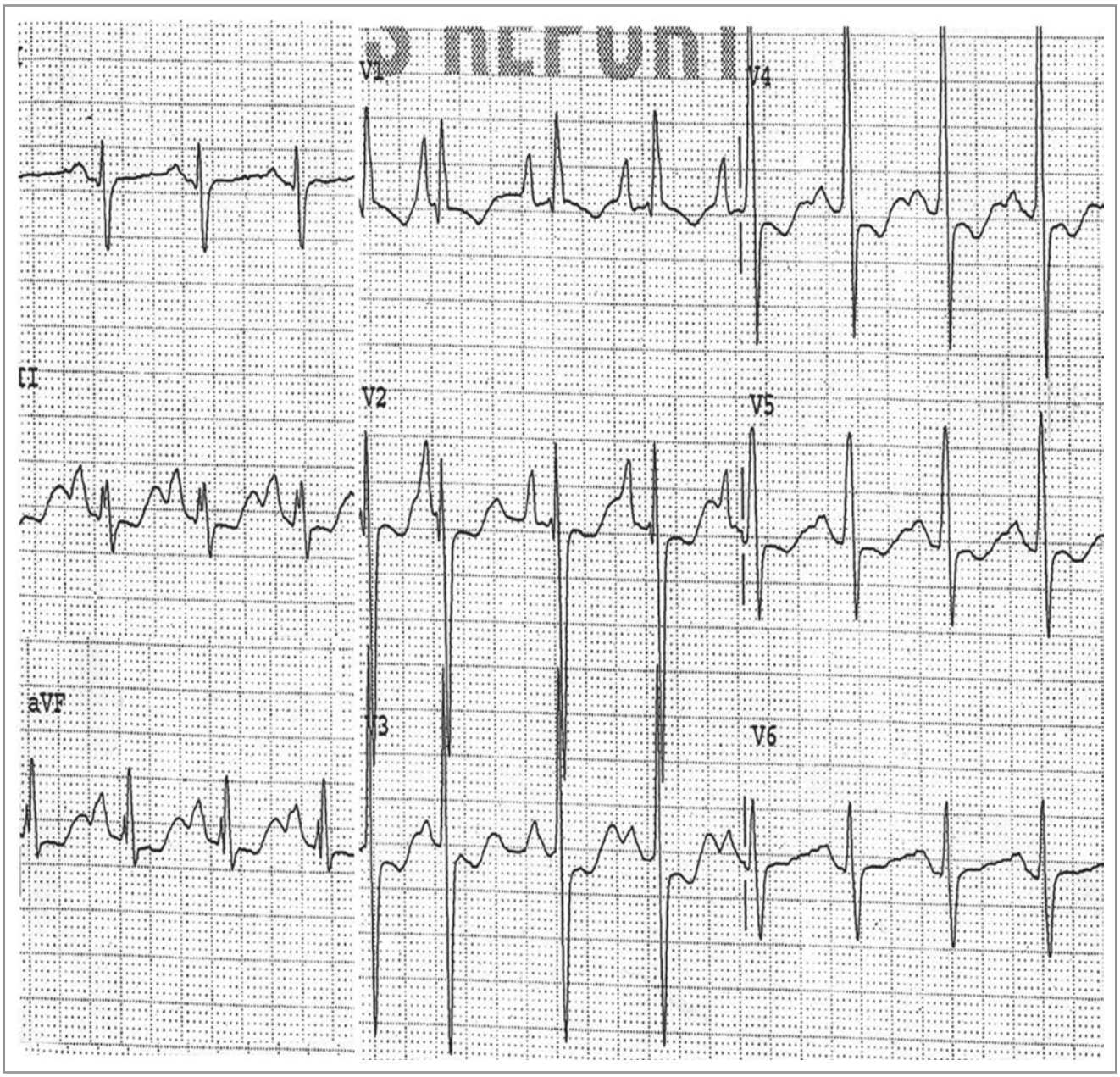


FIGURE 30-16

Combined ventricular hypertrophy and *right atrial abnormality/hypertrophy/enlargement*

MYOCARDIAL INFARCTION (TABLE 30-1)

A. **Acute MI**

■ Progression of ECG changes during an acute MI:

1. Earliest changes of MI are tall, peaked and **symmetric** (i.e. hyperacute) T waves due to localized hyperkalemia (Fig. 30-17a) and shortening of the QT interval due to intracellular hypercalcemia.
2. ST segments become elevated and are initially concave (Fig. 30-17b).
3. ST segments elevate further and become convex, merging with the T wave. This is called a **current of injury** (Fig. 30-17c) and looks similar to a monophasic action potential.

TABLE 30-1

TYPES OF ST-T WAVE ABNORMALITIES IN PATIENTS WITH MYOCARDIAL ISCHEMIA, INJURY, OR INFARCTION

ST/TW WAVE ABNORMALITIES	ECG CHANGES
Myocardial ischemia	■ Horizontal or downsloping **ST segment depression** may be upsloping if ST depression >1.5 mm 80 msec after J point ■ T waves are typically inverted ■ No Q waves present
Myocardial injury	■ **ST segment elevation** ■ Reciprocal ST depressions may be seen in other uninvolved leads ■ T waves are typically peaked (and **symmetric**) or merged with the ST segment ■ No Q waves present
Myocardial infarction—age recent or probably acute	■ **ST segment elevation** ■ T waves may be peaked (and **symmetric**), appear normal, or inverted ■ **Presence of Q waves**
Myocardial infarction—age indeterminate or probably old	■ ST segments are isoelectric ■ T waves may be normal, inverted or non-specifically altered ■ **Presence of Q waves**

4. Reciprocal ST segment depression is seen in other non-infarct leads.
5. Q waves develop with loss of R waves (Fig. 30-17d) heralding infarction.
6. As ST segment returns to baseline, Q waves become deeper and T waves invert (chronic infarct pattern; Fig. 30-17e).

■ Persistent ST elevation months or longer after the acute event indicates an aneurysm of infarcted wall.

■ Location of acute MI:

– Inferior MI (Fig. 30-18)—ST elevation in II, III, aVF.
– Posterior MI (Fig. 30-18)—ST depressions in V1–V2 associated with an inferior wall MI. Confirmed with ST elevations in posterior leads (V7–V9).
– RV MI—ST elevations in V1–V2 associated with an inferior wall MI. Confirmed with ST elevation in right-sided leads rV3–rV4.
– Anteroseptal MI—ST elevation in V1–V2.
– Anteroapical MI—ST elevation in V3–V4
– Anterolateral MI—ST elevation in V5–V6.
– Lateral MI—ST elevation in I, aVL.

B. **Chronic MI**

■ Chronic MI is identified by the presence of abnormal Q waves, usually with associated T wave inversions.

■ Abnormal Q waves include:

– Any Q wave > 0.02 s or any QS complex in leads V2–V3.
– Any Q wave ≥0.03 s and ≥1 mm in depth or any QS complex in any two contiguous leads (I, aVL; V1–V6; II, III, aVF).
– Exceptions

■ Q waves or QS complexes in lead V1 may be considered normal.
■ Isolated Q waves in lead III are considered normal.
■ Isolated Q waves in lead aVL are considered normal if the axis is between 60° and 90°.

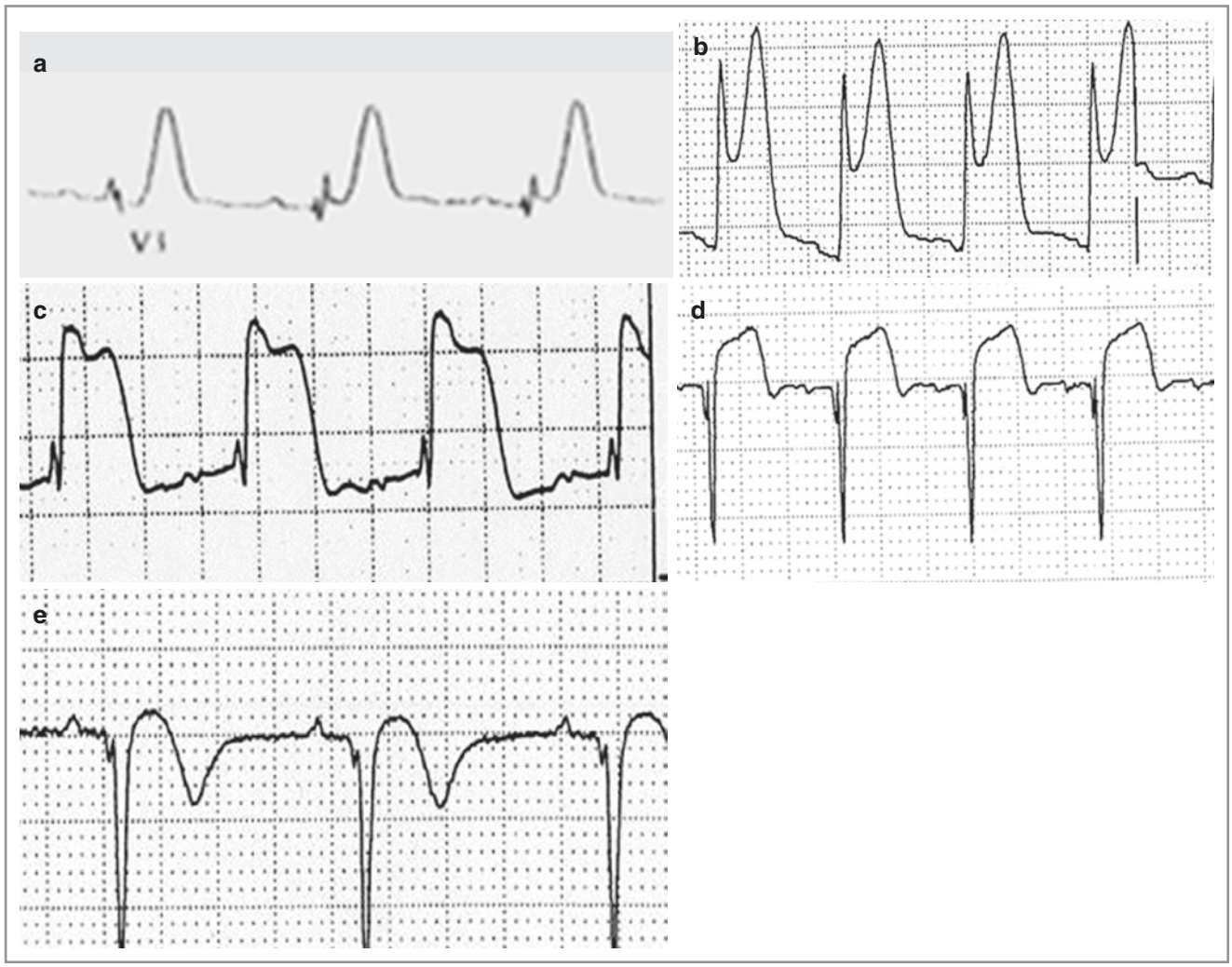


FIGURE 30-17

Stages of acute myocardial infarction characterized by (**a**) hyperacute T waves, (**b**) concave ST-segment elevation and (**c**) convex ST-segment elevation and merging with the T wave (a **current of injury**, *ST and/or T wave abnormalities suggesting myocardial injury*); (**d**, **e**) development of Q waves herald the onset of infarction with subsequent T wave inversion and return of ST segments to baseline (*age recent, or probably acute myocardial infarction*).

- Location of chronic MI:
  - Inferior MI—Q waves in II, III, aVF (Fig. 30-19a).
  - Anteroseptal MI—Q waves in V1–V2 (Fig. 30-19b).
  - Anteroapical MI—Q waves in V3–V4.
  - Anterolateral MI—Q waves in V5–V6.
  - Lateral MI—Q waves in I, aVL.
  - Posterior MI—Tall R wave in V1 and V2 (R/S > 1) with duration > 0.04 s. Typically seen in association with chronic inferior MI and in the absence of other etiologies for tall R waves in V1 (see "Right Ventricular Hypertrophy").

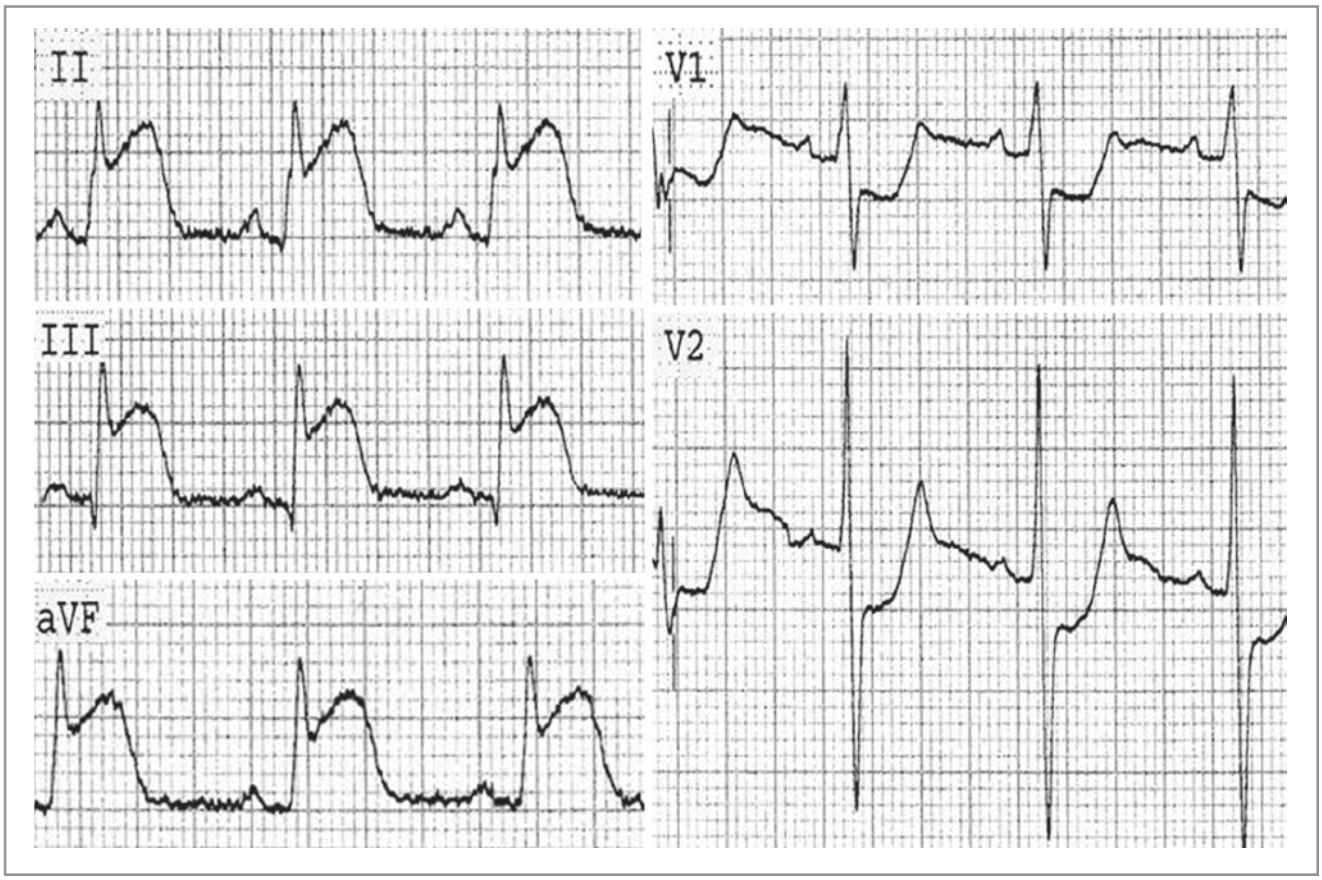


FIGURE 30-18

Inferior and *posterior age recent, or probably acute myocardial infarction*

PERICARDITIS

■ Characteristic stages of pericarditis:

- **Stage 1**—Diffuse, concave up, ST segment elevation in almost all leads except aVR (and sometimes V1) which shows ST segment depression (Fig. 30-20). There may also be associated PR segment depression (and PR segment elevation in leads with ST segment depression). In contrast to acute MI, T waves are normal and there are no reciprocal ST segment changes.
- **Stage 2**—Normalization of PR and ST segments.
- **Stage 3**—Development of diffuse T wave inversions after ST segments return to their isoelectric baseline.
- **Stage 4**—Normalization of the ECG.

CONDUCTION ABNORMALITIES

A. **Sinus node pause**

■ A pause in rhythm with no P wave during the pause.
■ **Sinus node arrest** (Fig. 30-21a)

- Failure of impulse formation at the sinus node.
- Duration of pause is **unrelated to the underlying sinus rate** (i.e. it is not a multiple of the preceding PP interval).

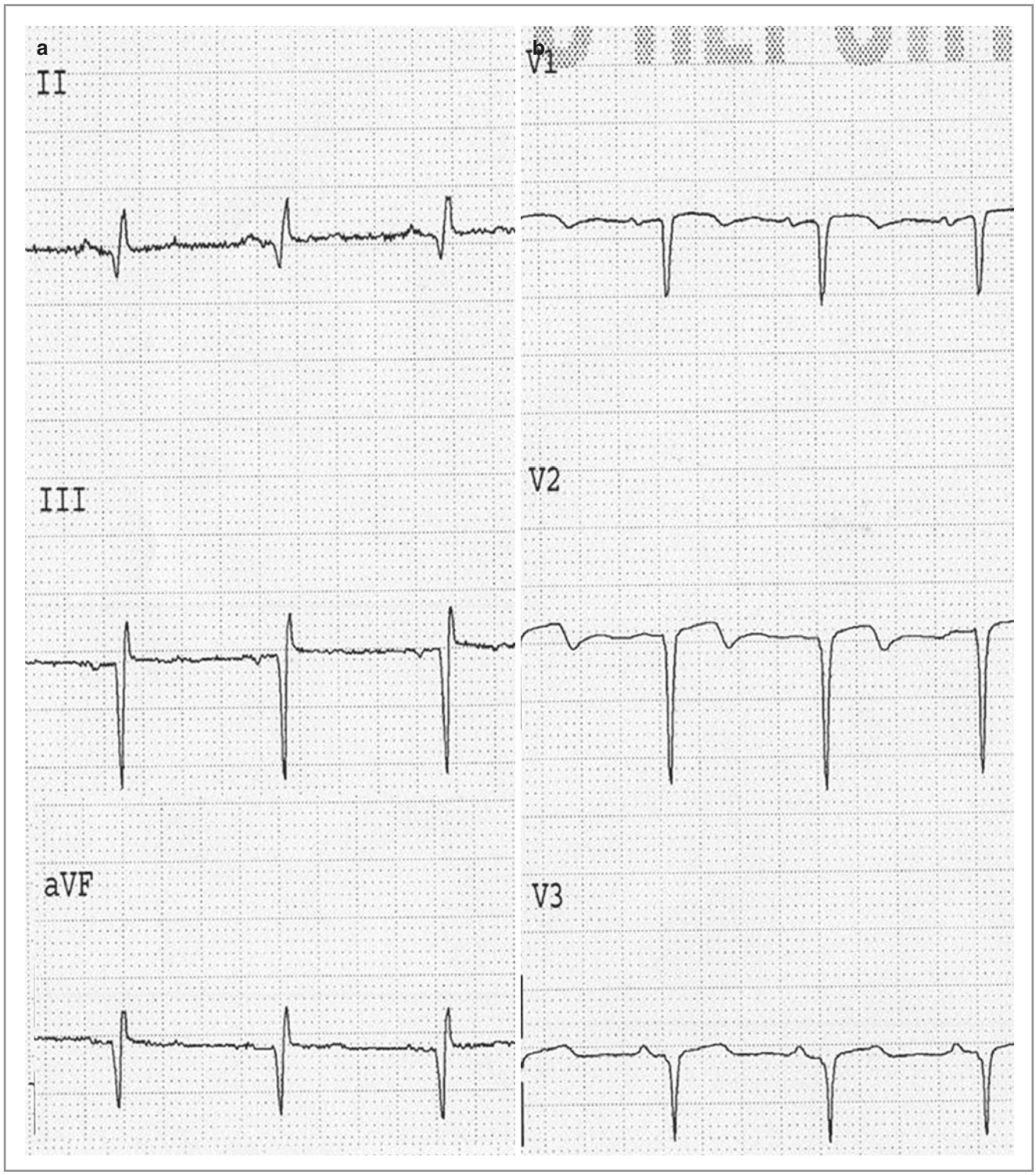


FIGURE 30-19

(**a**) *Inferior age indeterminate, or probably old myocardial infarction*; (**b**) anterior or anteroseptal age indeterminate, or probably old myocardial infarction

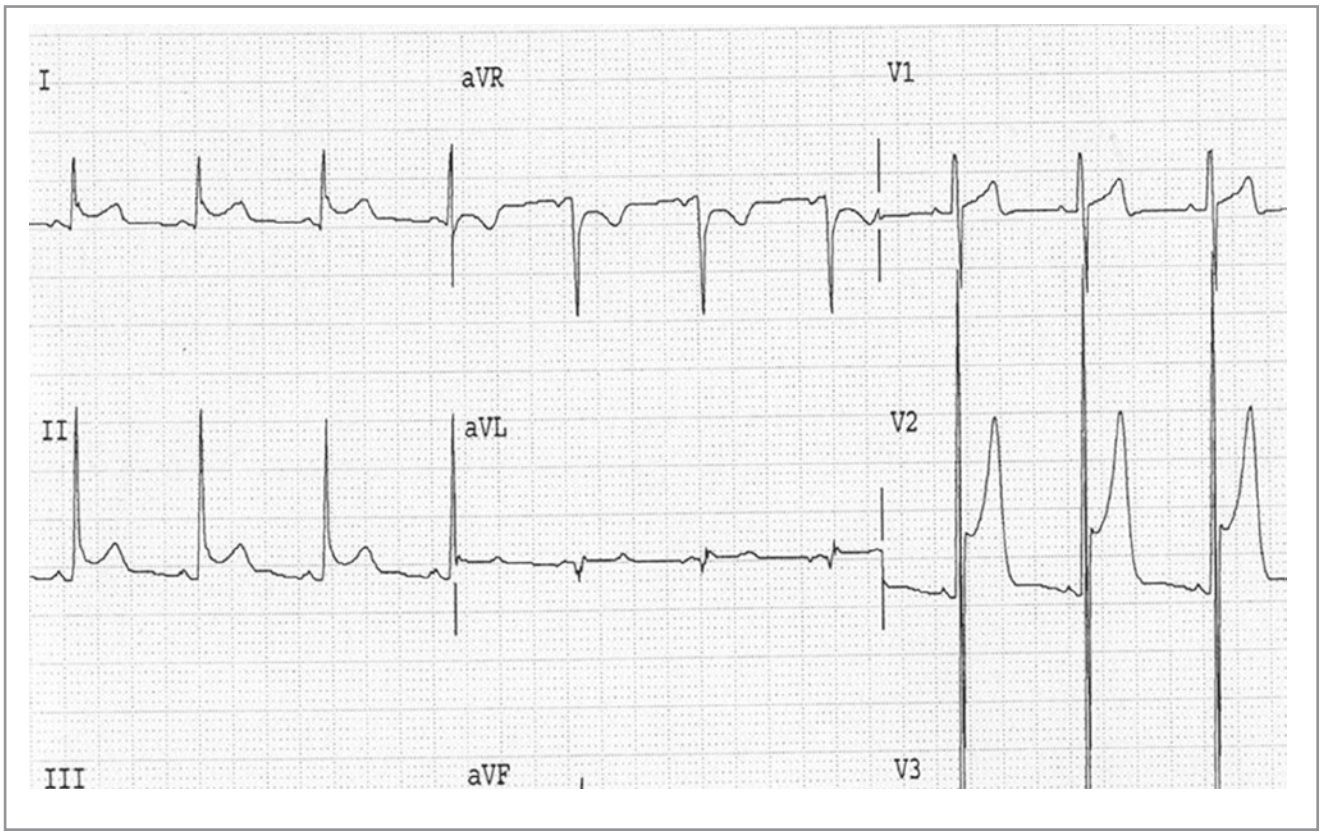


FIGURE 30-20

Acute pericarditis

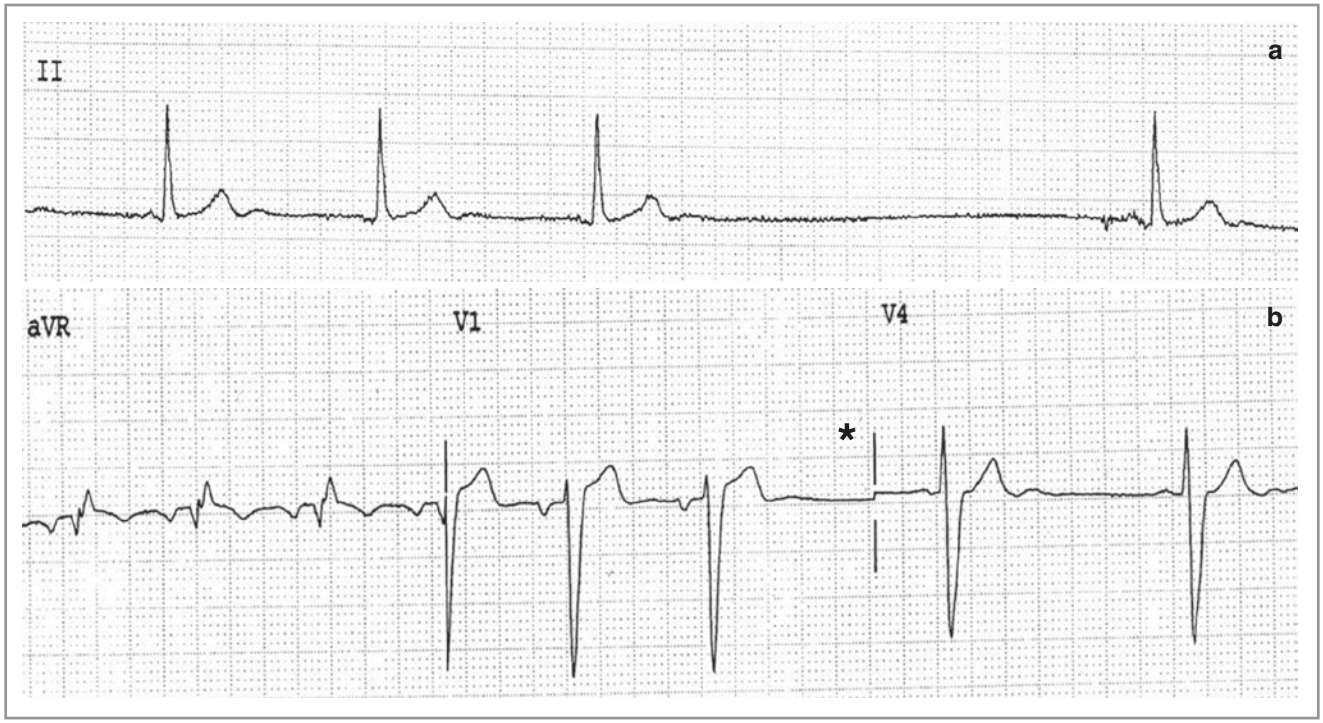


FIGURE 30-21

(**a**) *Sinus pause or arrest*; (**b**) *sinoatrial exit block*. Note that the pause denoted by * is exactly two P-P intervals

- **Sinus node exit block** (Fig. 30-21b)
  - Sinus node generates an impulse, but there is no atrial capture (and therefore, no P wave).
  - Duration of pause (PP interval) is a multiple of the underlying sinus rate (usually 2 sinus intervals).

B. **First degree AV block** (Fig. 30-22)

- Defined by prolonged PR interval (>0.20 s) and therefore, prolonged AV conduction.
- PR interval varies with autonomic tone, shortening with sinus tachycardia and lengthening with sinus bradycardia.

C. **Second degree AV block**

- **Mobitz type I (Wenckebach;** Fig. 30-23)
  - Progressive PR interval prolongation before a single nonconducted P wave and pause with subsequent shortening of PR interval (to baseline).
  - Due to abnormal conduction through the AV node.
- **Mobitz type II** (Fig. 30-24)
  - Stable PR interval before and after nonconducted P wave and pause.
  - There may be one or more consecutive nonconducted P waves.
  - Due to abnormal conduction in the His-Purkinje system.
- **2:1 AV block** (Fig. 30-25)
  - Every other P wave is nonconducted with a stable PR interval.
  - May be Mobitz I or Mobitz II, which is most easily discerned by examining prior ECGs or other parts of the current ECG for changes in the pattern of conduction (i.e. if 2 or more sequentially conducted P waves with same PR interval or development of complete heart block with escape ventricular rhythm it is Mobitz II; if two or more sequentially conducted P waves with prolonging PR interval and then nonconducted P wave or if with complete heart block there is an escape junctional rhythm it is Mobitz I)

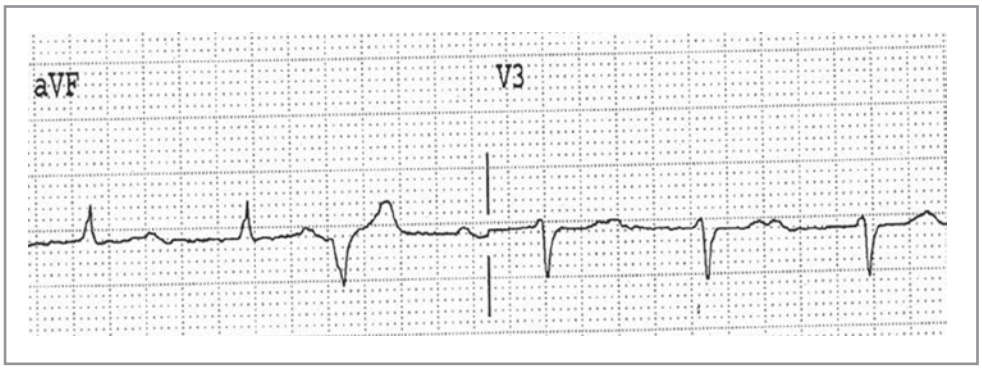


FIGURE 30-22

AV block, 1°

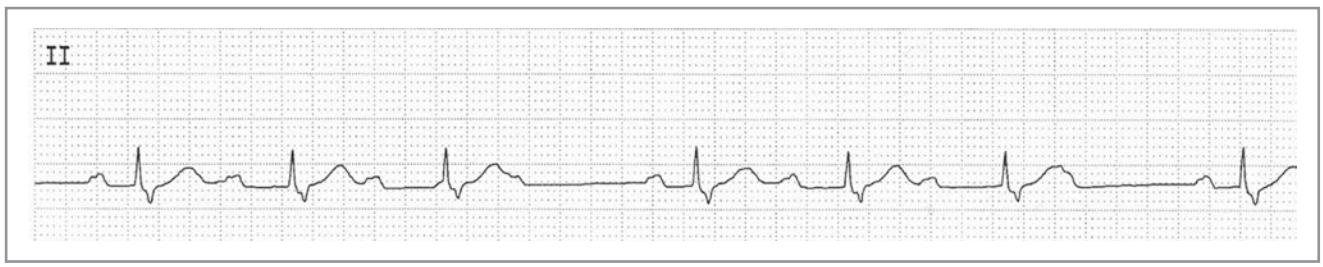


FIGURE 30-23

AV block, 2°–Mobitz type I (Wenckebach)

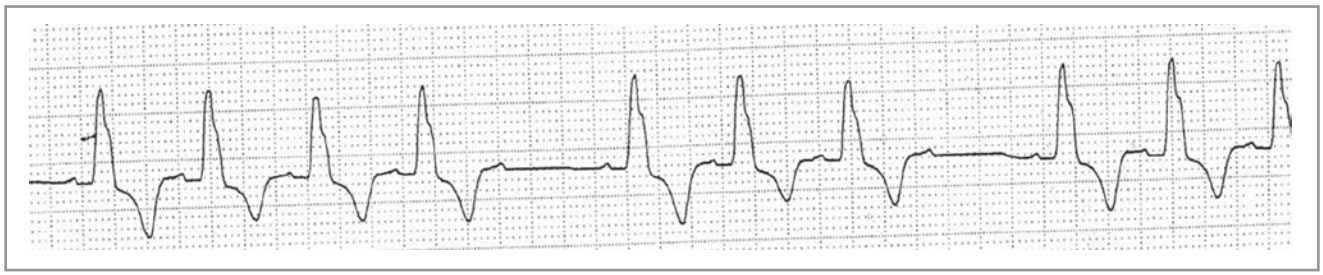


FIGURE 30-24

AV block, 2°–Mobitz type II

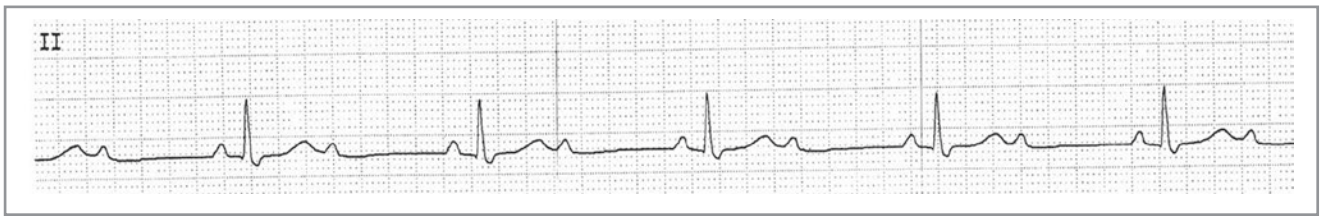


FIGURE 30-25

AV block, 2:1

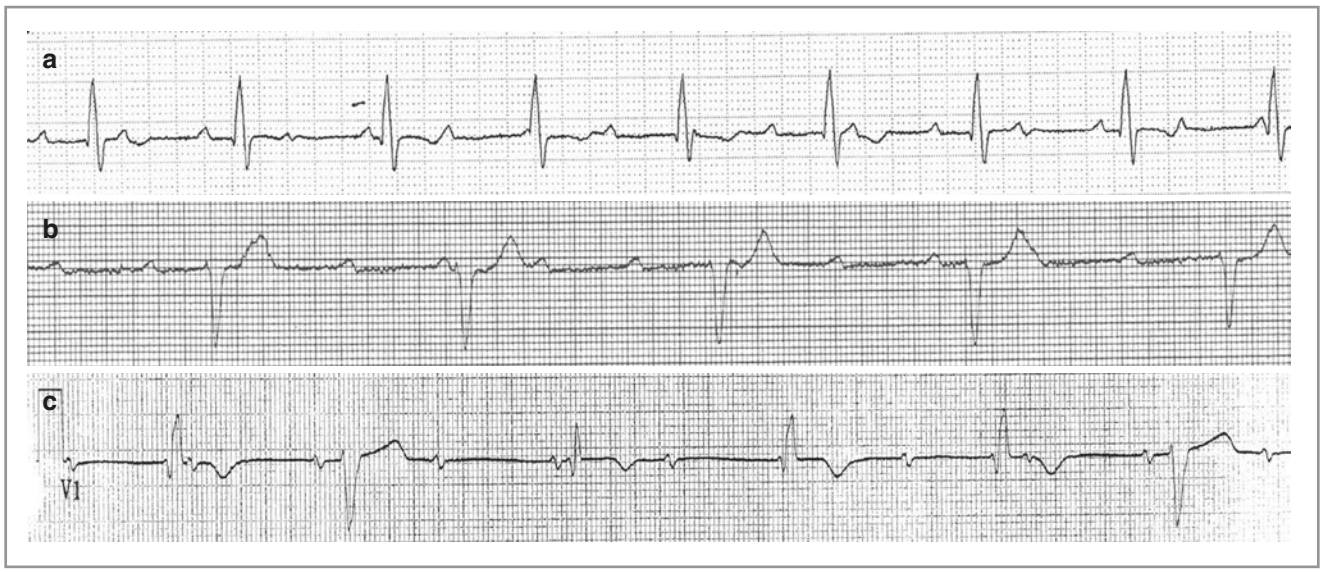


FIGURE 30-26

AV block, 3° (complete heart block) with (**a**) *AV junctional rhythm*, (**b**) *ventricular escape rhythm* and (**c**) *ventricular escape rhythm* with intermittent capture/fusion

- P wave morphology and PP intervals are constant for all of the above.
- First degree AV block may also be present.

D. **Third degree AV block (complete heart block;** Fig. 30-26)

- No association between P waves and QRS complexes (i.e. AV dissociation) due to an absence of atrioventricular conduction (i.e. PR intervals are variable).
- Atrial rate > ventricular rate.
  - In comparison, **AV dissociation** (atrial rate < ventricular rate) is due to an accelerated junctional or ventricular rhythm and **not due to complete heart block**.

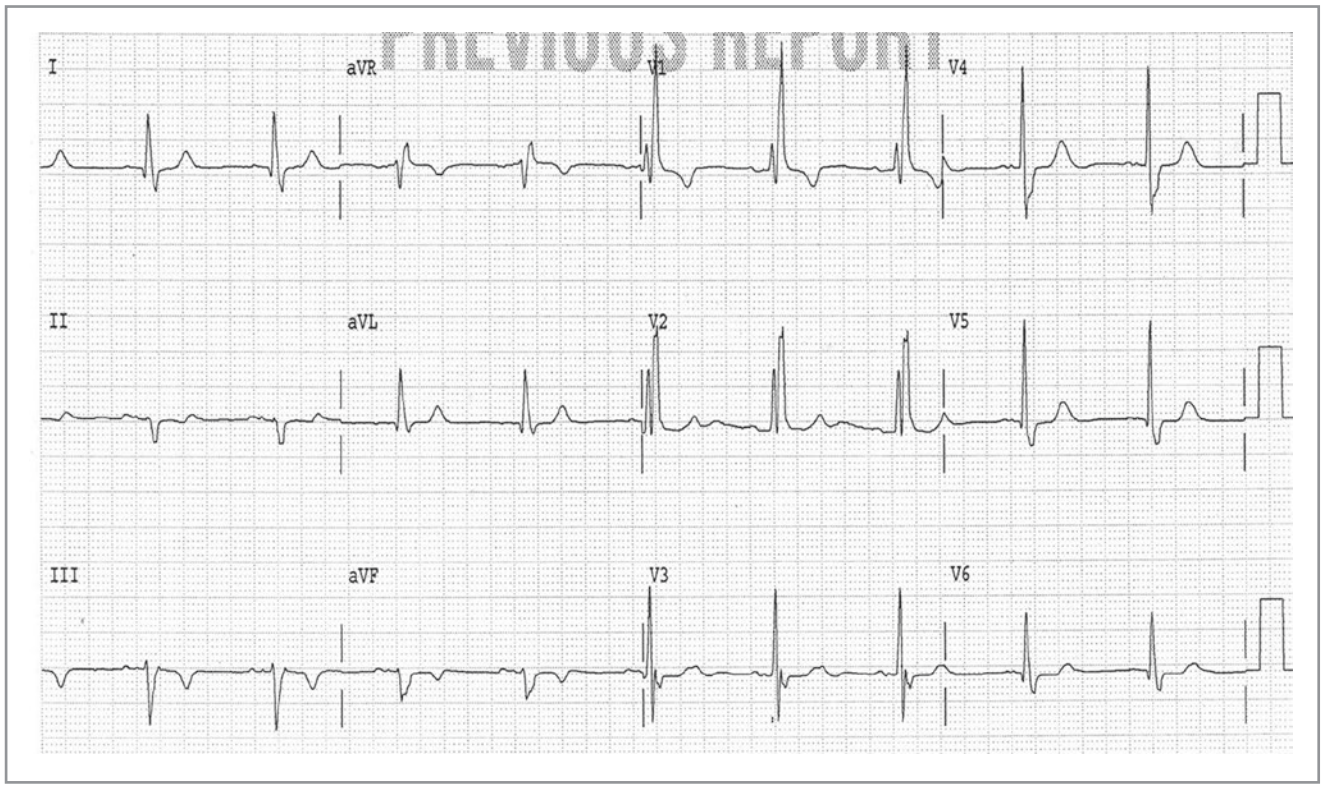


FIGURE 30-27

RBBB, complete

- Etiology of escape rhythm based on QRS morphology and not rate.
- Intermittent capture may occasionally be present (Fig. 30-26c).

E. **Right bundle branch block** (Fig. 30-27)

- QRS duration ≥ 0.12 s due to delayed activation of RV (via left bundle and directly through RV myocardium).
- rSR' complex in lead V1–V2 and broad S wave in leads I, V5, and V6.
- Abnormal RV repolarization results in secondary ST-T wave changes seen in V1–V3.
- RV activation is abnormal, therefore RV abnormalities (e.g. RVH) cannot be recognized.
- LV activation is normal (initial portion of the QRS complex is normal), therefore LV abnormalities can be recognized (e.g. LVH, infarction, pericarditis).
- LAFB or LPFB may also be present (i.e. bifascicular block).

F. **Left bundle branch block** (Fig. 30-28)

- QRS duration ≥ 0.12 s due to delayed activation of LV (via right bundle and directly through LV myocardium).
- Broad tall R wave in leads I, aVL, V5, and V6 with deep rS or QS complexes in V1–V2.
- No Q waves in I, aVL, V5 and V6 (absence of septal forces as septal branch comes from left bundle).
- No S waves in I and V6 (all forces are directed right to left).
- Diffuse ST-T wave abnormalities are present, usually with deflections opposite that of the QRS complex.
- Axis is normal or leftward (axis cannot be rightward or indeterminate).
- Since LV activation is abnormal, LV abnormalities cannot be recognized.

G. **Intraventricular conduction delay (IVCD;** Fig. 30-29)

- Nonspecific QRS widening (QRS duration ≥ 0.10 s) without specific bundle branch block pattern due to diffuse slowing of conduction through the normal His-Purkinje system.

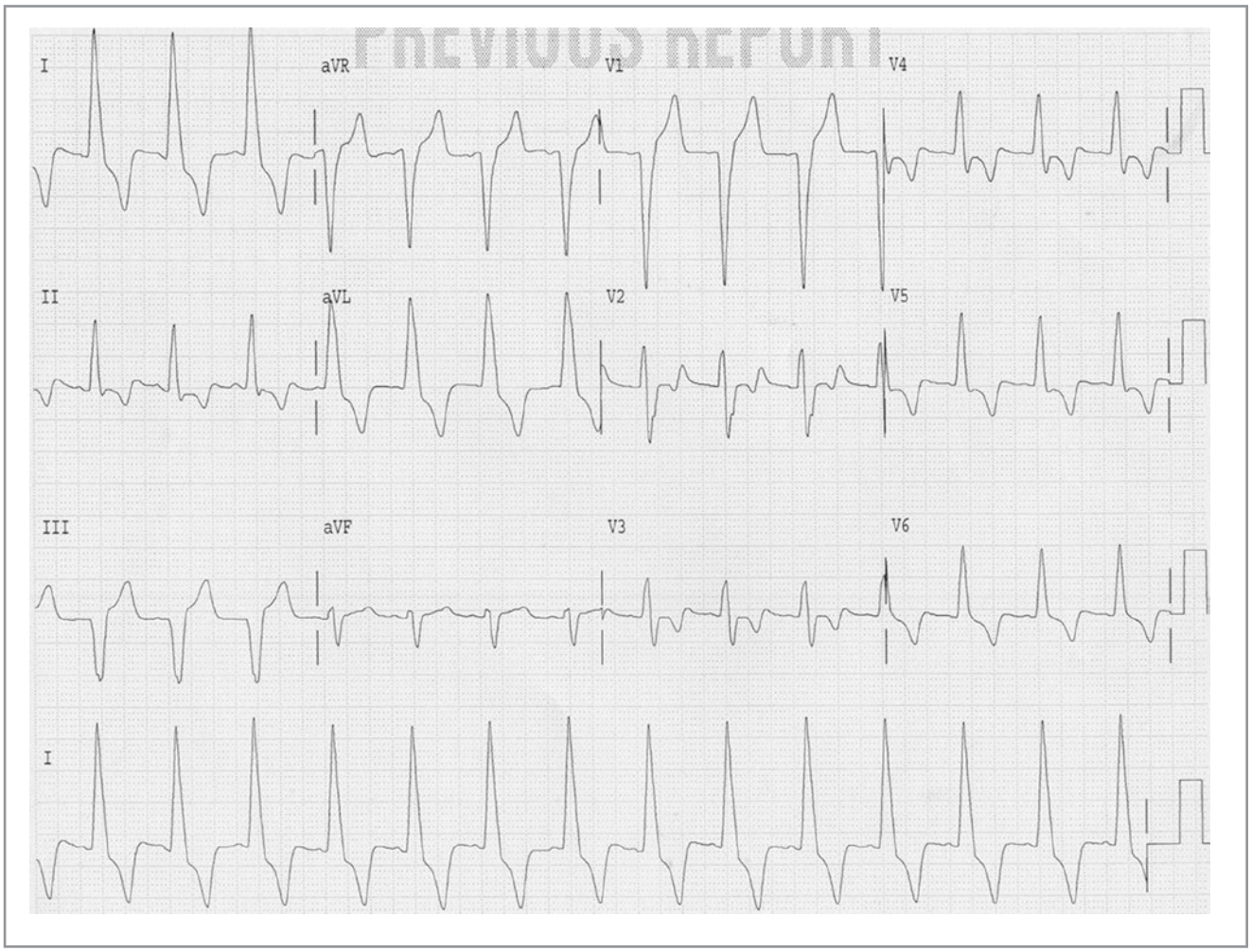


FIGURE 30-28

LBBB, complete

- Since there is still conduction through the His-Purkinje system (albeit slowed), abnormalities of both ventricles can still be diagnosed.
- "Incomplete blocks" should be considered part of the IVCD spectrum as bundle conduction is "all or none" and not incomplete.
  - **Incomplete RBBB**—RBBB morphology (rSR' in lead V1) with QRS duration ≥0.10 s and <0.12 s.
  - **Incomplete LBBB**—LBBB morphology with QRS duration ≥0.10 s and <0.12 s.

PRE-EXCITATION PATTERN

A. **Wolff-Parkinson-White (WPW;** Fig. 30-30a)

- Short PR interval with a widened QRS complex due to initial conduction via an accessory pathway (bundle of Kent) between atrial and ventricular myocardium.
  - QRS is widened at its base as a result of a delta wave (early, but slow myocardial activation via the accessory pathway fusing with activation via the normal AV-His-Purkinje system).

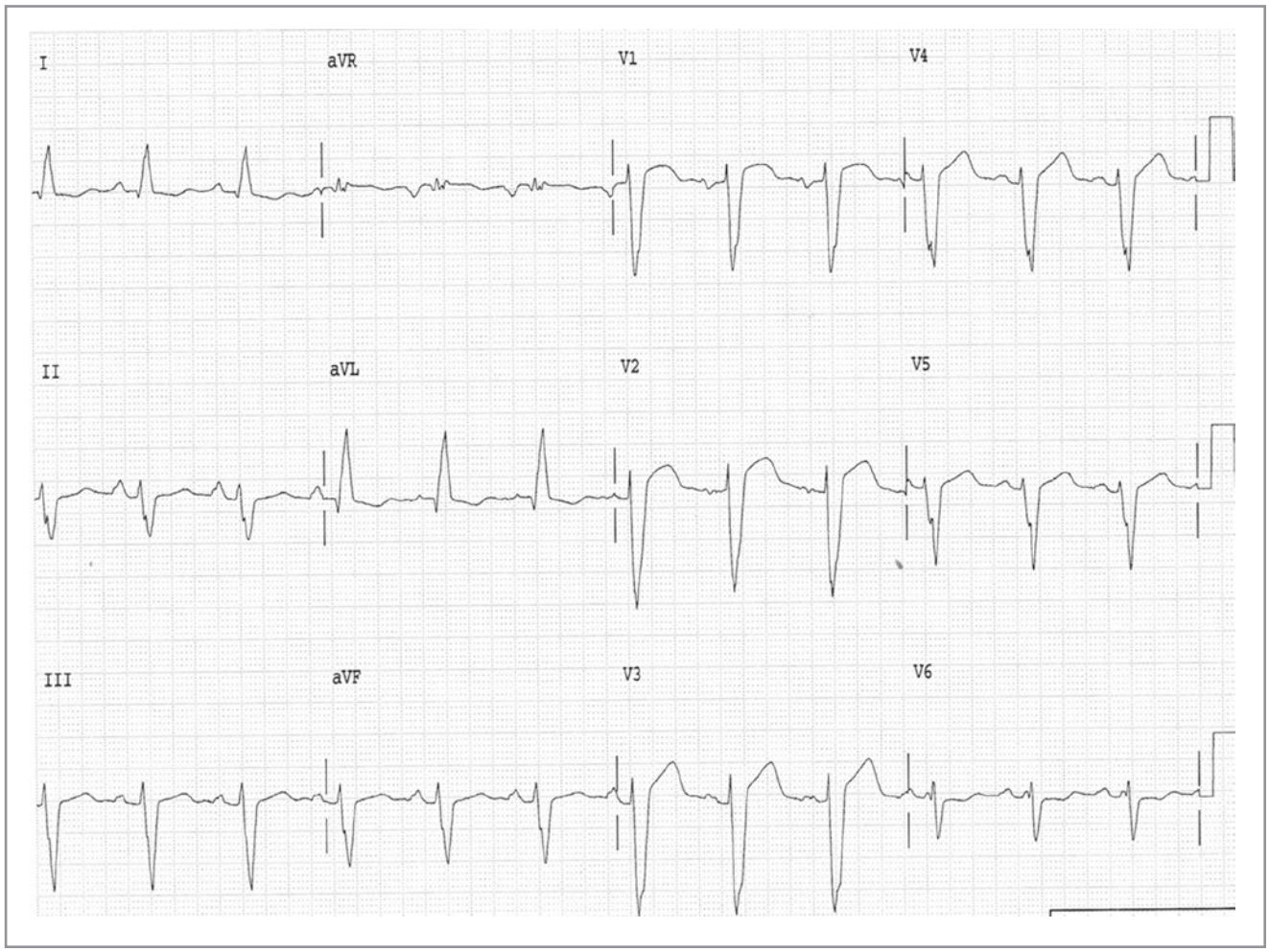


FIGURE 30-29

Intraventricular conduction disturbance, nonspecific type in the setting of a dilated cardiomyopathy

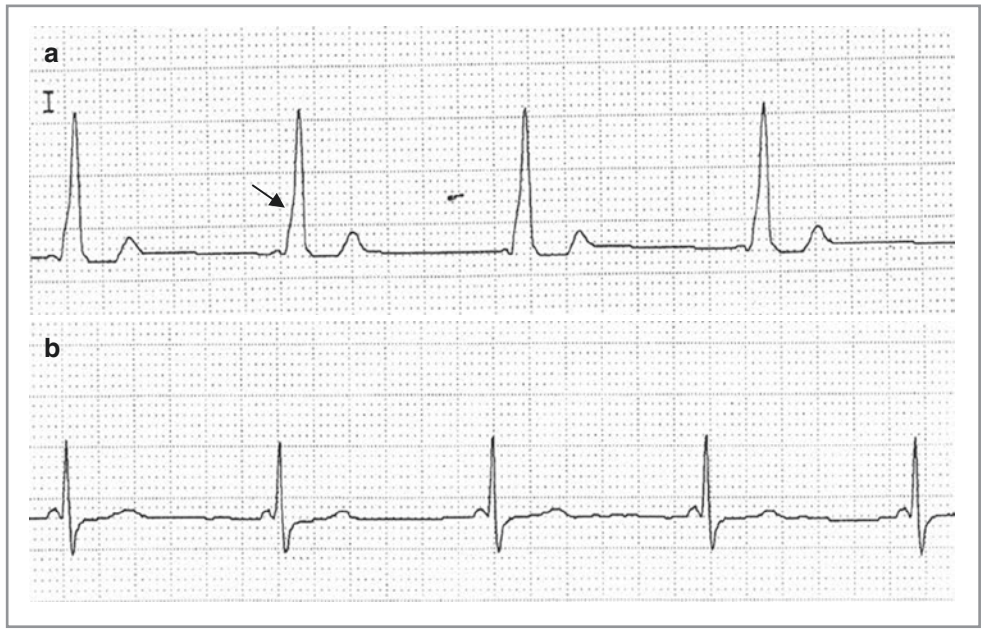
- Arrhythmias may occur in patients with WPW, including most commonly atrioventricular reentrant tachycardia (AVRT), atrial tachycardia, atrial flutter and atrial fibrillation.
- Atrial fibrillation is of particular concern as very rapid ventricular rates due to rapid conduction via the accessory pathway can precipitate ventricular fibrillation. Needs to be distinguished from rate-related aberration before therapy is initiated.
  - In WPW with atrial fibrillation, there is no association between QRS width and heart rate (i.e. seen are narrow QRS complexes at faster rates and wider QRS complexes at slower rates), whereas in rate-related aberrancy the QRS complex will widen at faster rates (see "Aberration", Fig. 30-31).

B. **Lown-Ganong-Levine (LGL;** Fig. 30-30b**)**

- Short PR interval with normal QRS width due to conduction via an accessory pathway (bundle of James) between the atrium and bundle of His.
- Has also been termed a "slick AV node."

FIGURE 30-30

(**a**) *Wolff-Parkinson-White pattern* in WPW syndrome. Arrow denotes the delta wave; (**b**) Lown-Ganong-Levine (LGL). Note the short PR interval without a delta wave



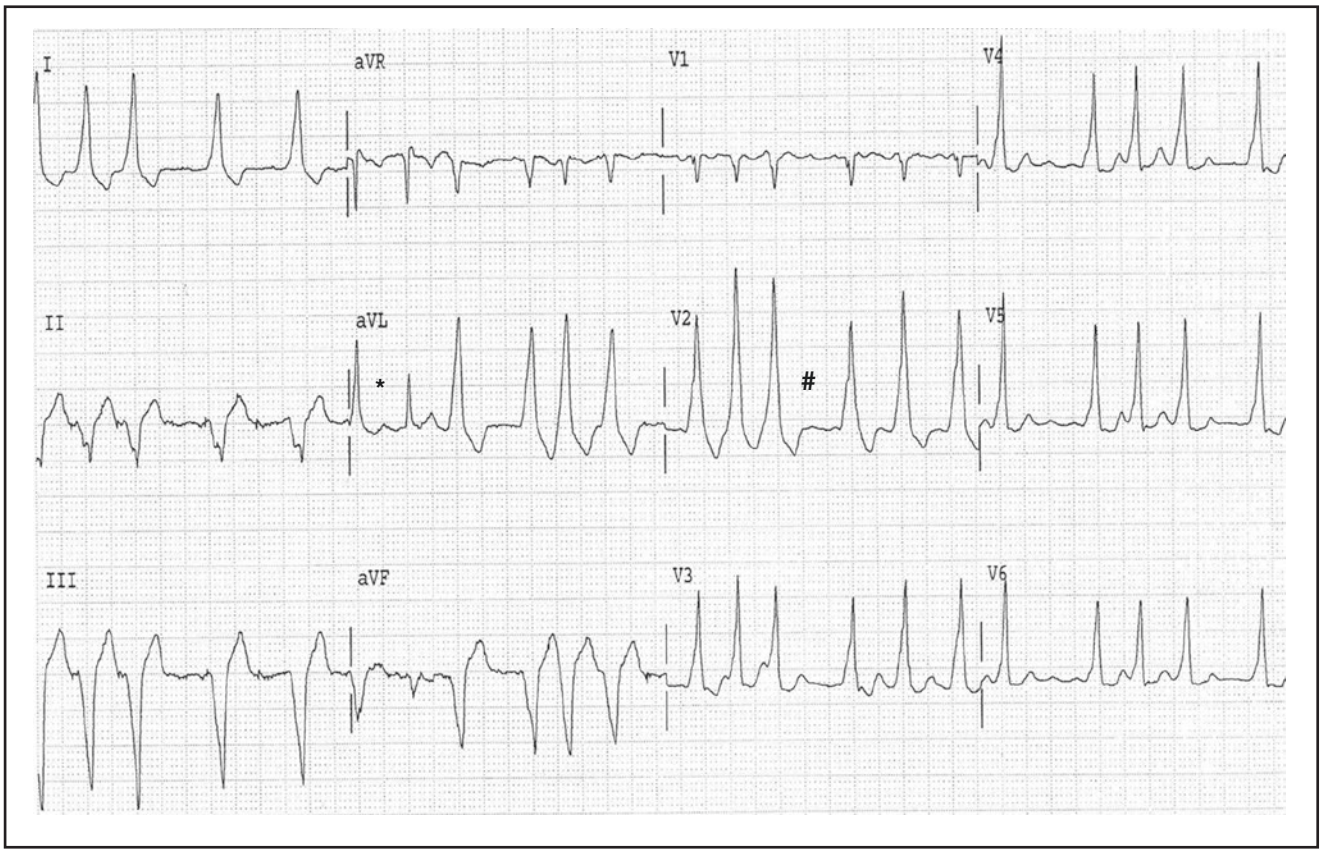


FIGURE 30-31

Atrial fibrillation with *Wolff-Parkinson-White pattern*. Note the width of the QRS complex does not respect a pattern of rate related aberration (compare the interval marked by ∗ with #)

SUPRAVENTRICULAR COMPLEXES AND RHYTHMS

A. **Sinus rhythm**

- P wave upright in leads I, II, aVF, V4–V6, and inverted in aVR.
- Uniform P wave morphology.
- PR intervals do not define sinus rhythm and so may be normal, prolonged or variable.
  - **Normal sinus rhythm**—Regular rhythm, rate 60–100 bpm.
  - **Sinus bradycardia**—Regular rhythm, rate < 60 bpm (Fig. 30-32a).
  - **Sinus tachycardia**—Regular rhythm, rate > 100 bpm (Fig. 30-32b).
  - **Sinus node reentry tachycardia**—Regular rhythm, rate >100 bpm. Unlike sinus tachycardia, however, rapid heart rates will have an abrupt onset and offset (rather than a gradual rise and fall).
  - **Sinus arrhythmia**—Irregularly irregular rhythm with heart rate variability due to respiration (i.e. respirophasic arrhythmia, Fig. 30-32c). Stable P wave morphology and PR interval.

B. **Premature atrial complex (PAC,** Fig. 30-33)

- Also known as premature atrial beat, atrial premature complex (APC), or atrial premature beat (APB).
- Early (premature) P wave followed by a normal (supraventricular) QRS complex. Rate related aberration may be present.
- P wave morphology and/or PR interval are different from that of sinus rhythm.
- Following the PAC there is a pause of variable duration which may be less than, the same as, or greater than 2 PP intervals.
- **Unifocal PACs**—Every PAC has the same abnormal P wave morphology.
- **Multifocal PACs**—Two or more different abnormal P wave morphologies associated with PACs.
- **Atrial bigeminy**—Every other QRS complex is a PAC.
- **Atrial trigeminy**—Every third QRS complex is a PAC.

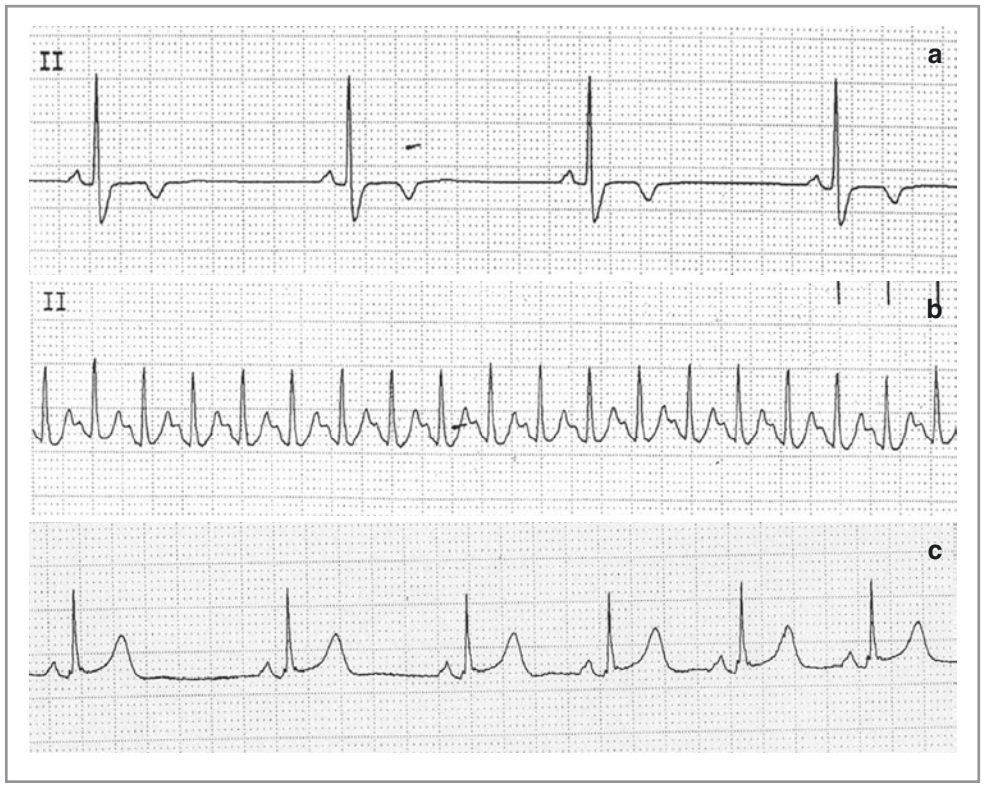
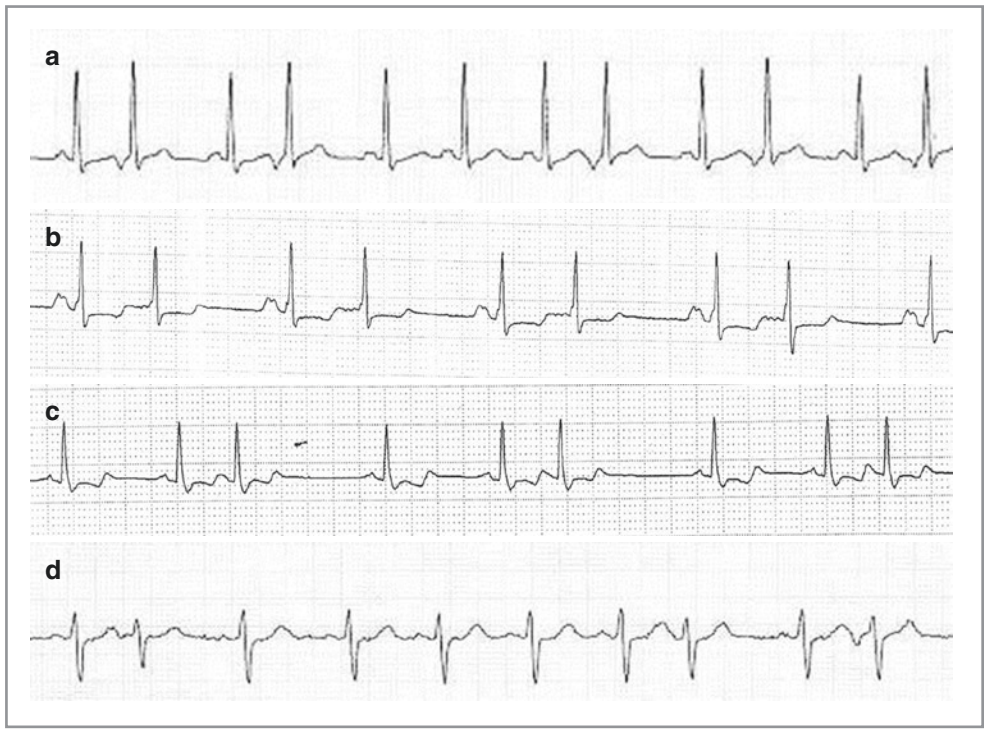


FIGURE 30-32

(**a**) *Sinus bradycardia*; (**b**) *sinus tachycardia*; (**c**) *sinus arrhythmia*

FIGURE 30-33

(**a**) Unifocal *atrial premature complexes*; (**b**) PACs in a bigeminy pattern; (**c**) PACs in a trigeminy pattern; (**d**) multifocal *atrial premature complexes*



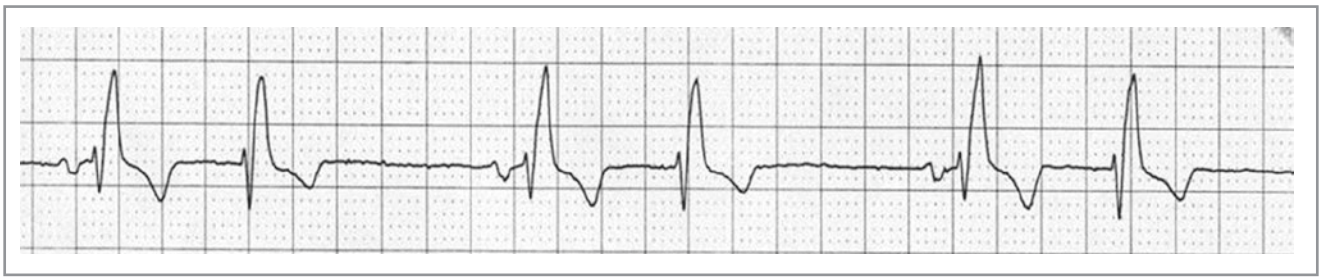


FIGURE 30-34

AV junctional premature complexes in a bigeminy pattern (and *RBBB, complete*)

C. **Premature junctional complex (PJC,** Fig. 30-34)

- Also known as premature junctional beat (PJB).
- P waves may follow or be contained within the QRS complex, but not precede them.
- Morphology of QRS complex is similar to that of sinus rhythm. Rate related aberration may be present.
- May also have a bigeminal or trigeminal pattern.

D. **Ectopic atrial rhythm** (Fig. 30-35a)

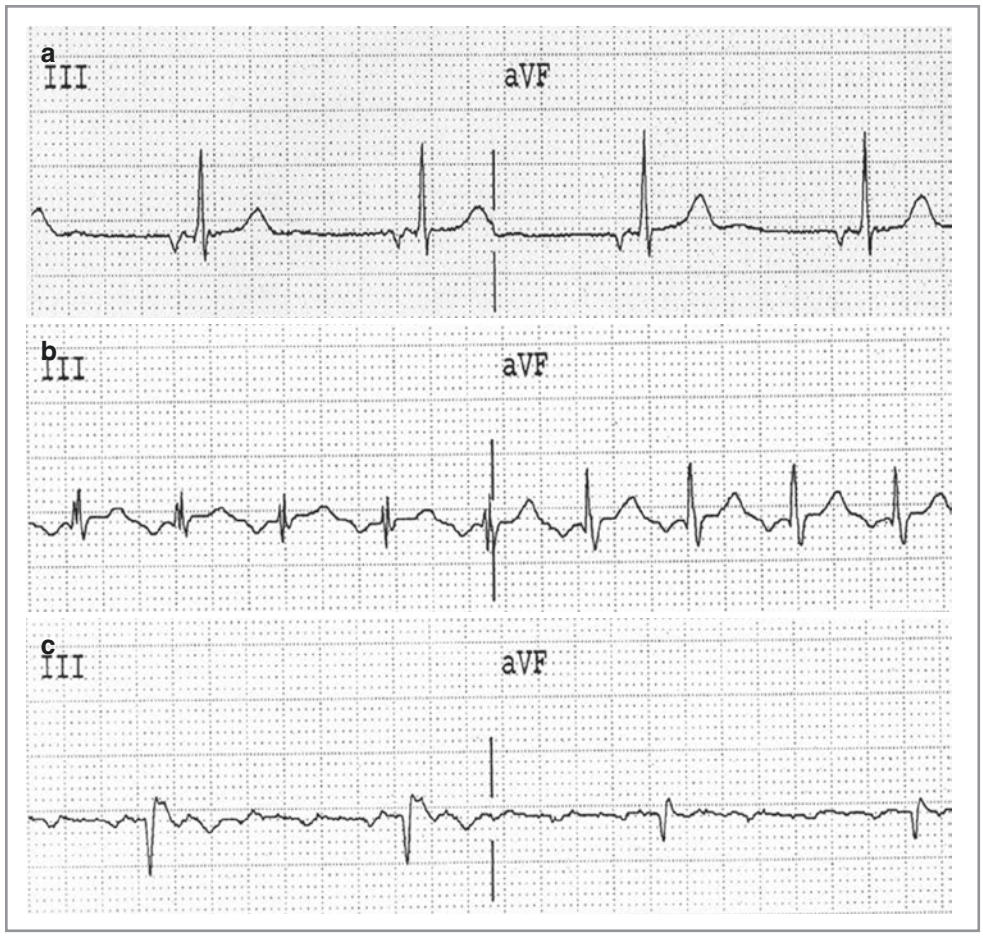
- Atrial rate is regular and <100 bpm.
- Distinct P waves of uniform morphology before each QRS complex. These are **different from sinus P waves**, but have a constant PR interval (that may be the same or different from sinus rhythm).
- QRS complexes are the same as those noted in sinus rhythm.

E. **Atrial tachycardia** (Fig. 30-35b)

- Atrial rate is regular with rates between 100 and 220 bpm.
- Distinct P waves of uniform morphology before each QRS complex. These are **different from sinus P waves**, but have a constant PR interval (that may be the same as or different from that of sinus rhythm).

FIGURE 30-35

(**a**) Ectopic atrial rhythm; (**b**) *atrial tachycardia*; (**c**) *atrial tachycardia* with 4:1 AV block—consider *digitalis toxicity, another AV nodal blocking agent or intrinsic AV nodal disease*



- If AV block is present (or an AV nodal blocking agent such as adenosine is used), an isoelectric baseline between sequential P waves will be seen.
- RR intervals can be regular or regularly irregular (if Wenckebach or a variable degree of AV block is present, Fig. 30-35c).

F. **Wandering atrial pacemaker** (Fig. 30-36a)

- Atrial and ventricular rates are irregularly irregular and <100 bpm.
- Presence of ≥3 different P wave morphologies (none of which are dominant) with variable PP, PR and RR intervals.

G. **Multifocal atrial tachycardia** (Fig. 30-36b)

- Atrial and ventricular rates are irregularly irregular and >100 bpm.
- Presence of ≥3 different P wave morphologies (none of which are dominant) with variable PP, PR and RR intervals.

H. **Atrial flutter** (Fig. 30-37)

- Flutter waves (i.e. 'F' waves) are uniform in morphology, amplitude and interval, with a continuously undulating baseline (i.e. there is no isoelectric baseline between the atrial waveforms).
- RR intervals can be regular or regularly irregular (if Wenckebach or a variable degree of AV block is present).
- Typical atrial flutter (Fig. 30-37a)
  - Flutter waves with atrial rates between 260 and 320 bpm.
  - Typically (but not always) negatively deflected in leads II, III, and aVF producing a "saw-tooth" baseline.

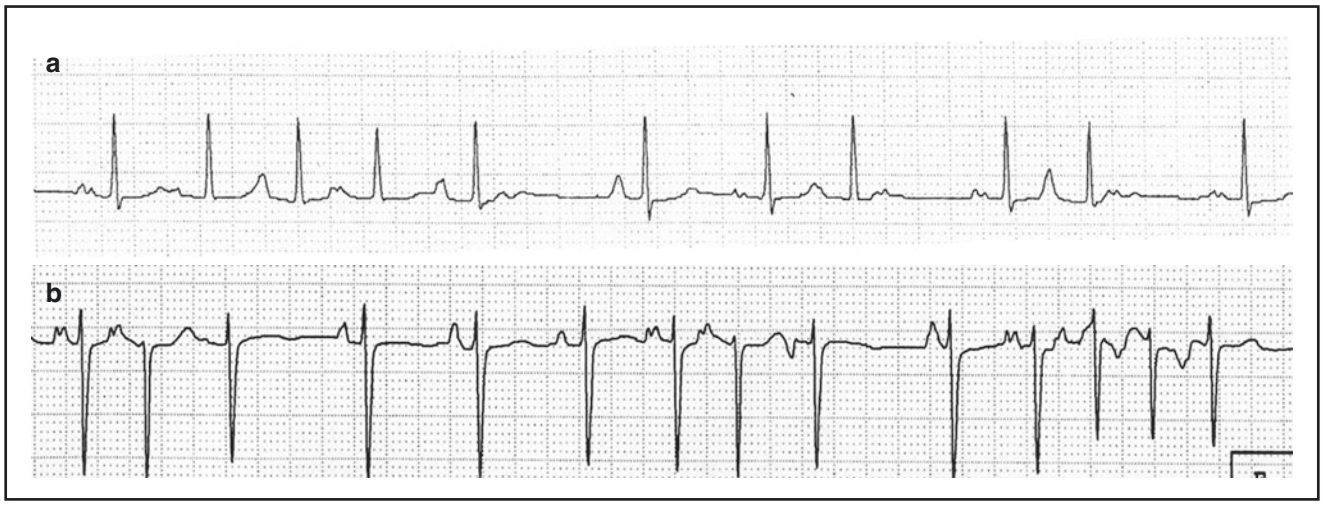


FIGURE 30-36

(**a**) Wandering atrial pacemaker; (**b**) *Atrial tachycardia, multifocal*

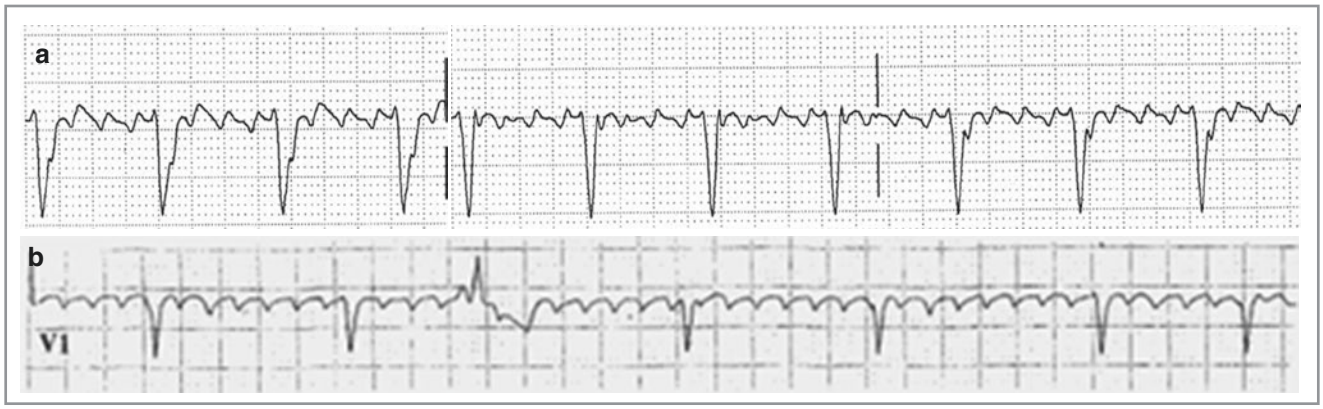


FIGURE 30-37

Atrial flutter—(**a**) typical and (**b**) atypical

- Atypical atrial flutter (Fig. 30-37b)
  - Flutter waves with a wide range of atrial rates, although usually > 320 bpm.
  - Typically (but not always) positively deflected in leads II, III and aVF.

I. **Atrial fibrillation** (Fig. 30-38)

- Characterized by fibrillatory waves which are variable in morphology, amplitude, and interval (atrial rates > 320 bpm and often > 450 bpm).
- No organized atrial activity or distinct P waves noted. Coarse fibrillatory waves seen when atrial fibrillation more recent in onset; the fibrillatory waves become finer as atrial fibrillation of longer duration.
- RR intervals are irregularly irregular with ventricular rates dependent on AV nodal conduction.

J. **Junctional (AV nodal) rhythms** (Fig. 30-39)

- Junctional rhythm—Rate ≤ 100 bpm.
- Junctional tachycardia—Rate > 100 bpm.
- Retrograde (inverted) P waves may be present following the QRS complex (due to ventriculoatrial [VA] conduction) with a stable RP interval or may be contained within the QRS complex.
- RR intervals are regular.

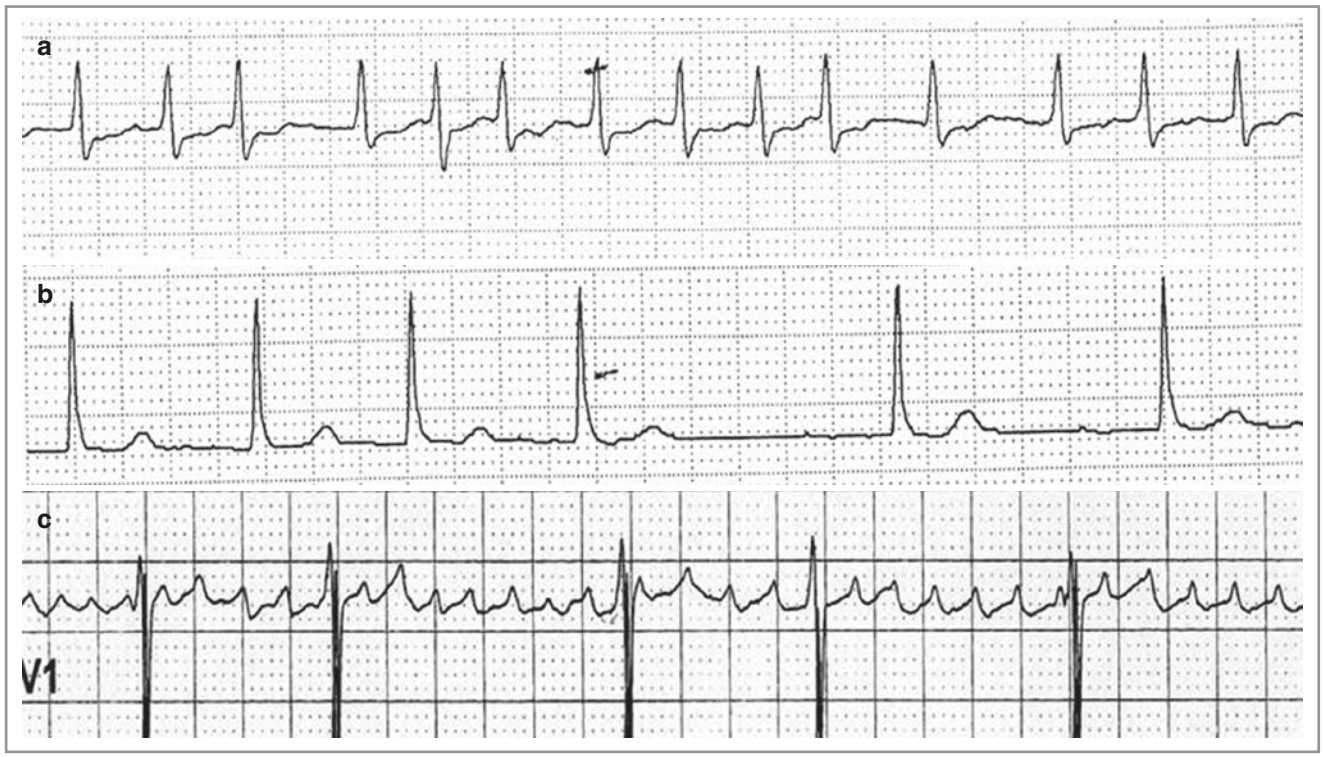


FIGURE 30-38

Atrial fibrillation with (**a**) rapid ventricular rate, (**b**) fine fibrillatory waves and (**c**) coarse fibrillatory waves

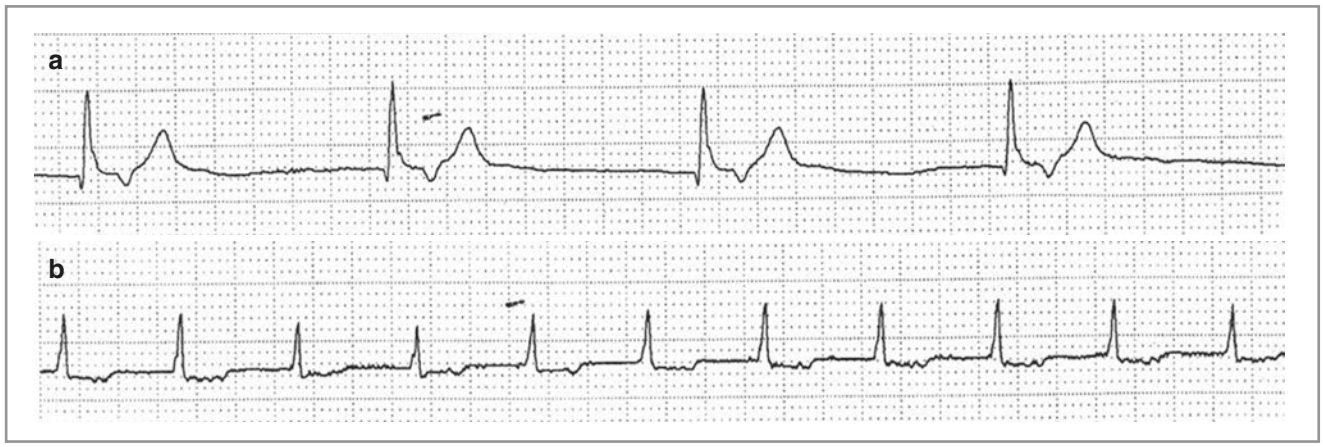


FIGURE 30-39

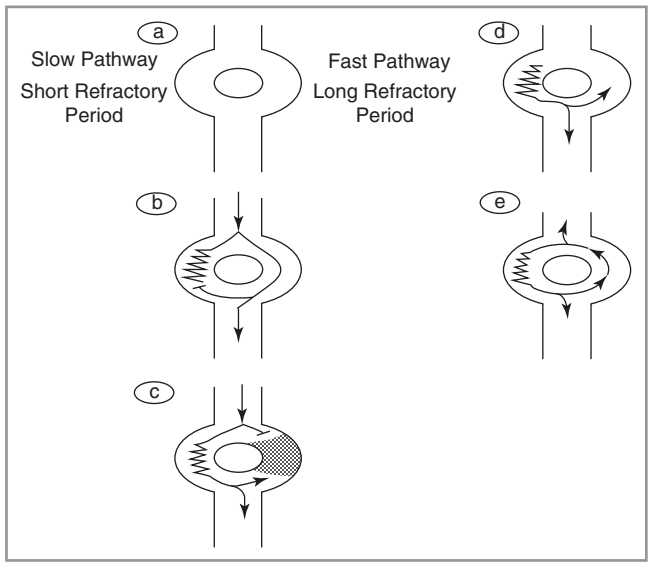
(**a**) *AV junctional rhythm* with retrograde P waves; (**b**) *AV junctional tachycardia*

K. **Atrioventricular nodal reentrant tachycardia (AVNRT)**

- A reentrant circuit within the AV node due to dual AV nodal pathways (fast conduction with a long refractory period, and slow conduction with a short refractory period).
- Regular rhythm with ventricular rates of 140–220 bpm.
- **Typical or common AVNRT** (*antegrade slow—retrograde fast*, Figs. 30-40 and 30-41)—The P wave may be superimposed on the end of the QRS complex and appear as an R' or S wave, or it may not be seen at all (no RP tachycardia). May have antegrade slow and retrograde slower than usual (termed slow-slow) in which case a retrograde P wave with short RP interval may be seen.
- **Atypical or uncommon AVNRT** (usually *antegrade fast—retrograde slow*).

FIGURE 30-40

Pathophysiology of AVNRT. (**a**) Dual AV nodal pathways—fast conduction with a long refractory period and slow conduction with a short refractory period; these two pathways are linked proximally and distally forming a cicuit (**b**) native conduction showing depolarization down both pathways; (**c**) a PAC is able to conduct down the slow pathway owing to the short refractory period, but is blocked in the fast pathway due to its long refractory period (shaded area); (**d**) If the fast pathway recovers by the time of arrival of the slow pathway at the distal portion of the circuit, this impulse will conduct retrograde to the atria via the fast pathway at the same time as antegrade conduction to the ventricles occurs through the slow pathway, (**e**) setting up a re-entrant circuit with antegrade conduction down the slow pathway and retrograde conduction via the fast pathway-termed slow-fast



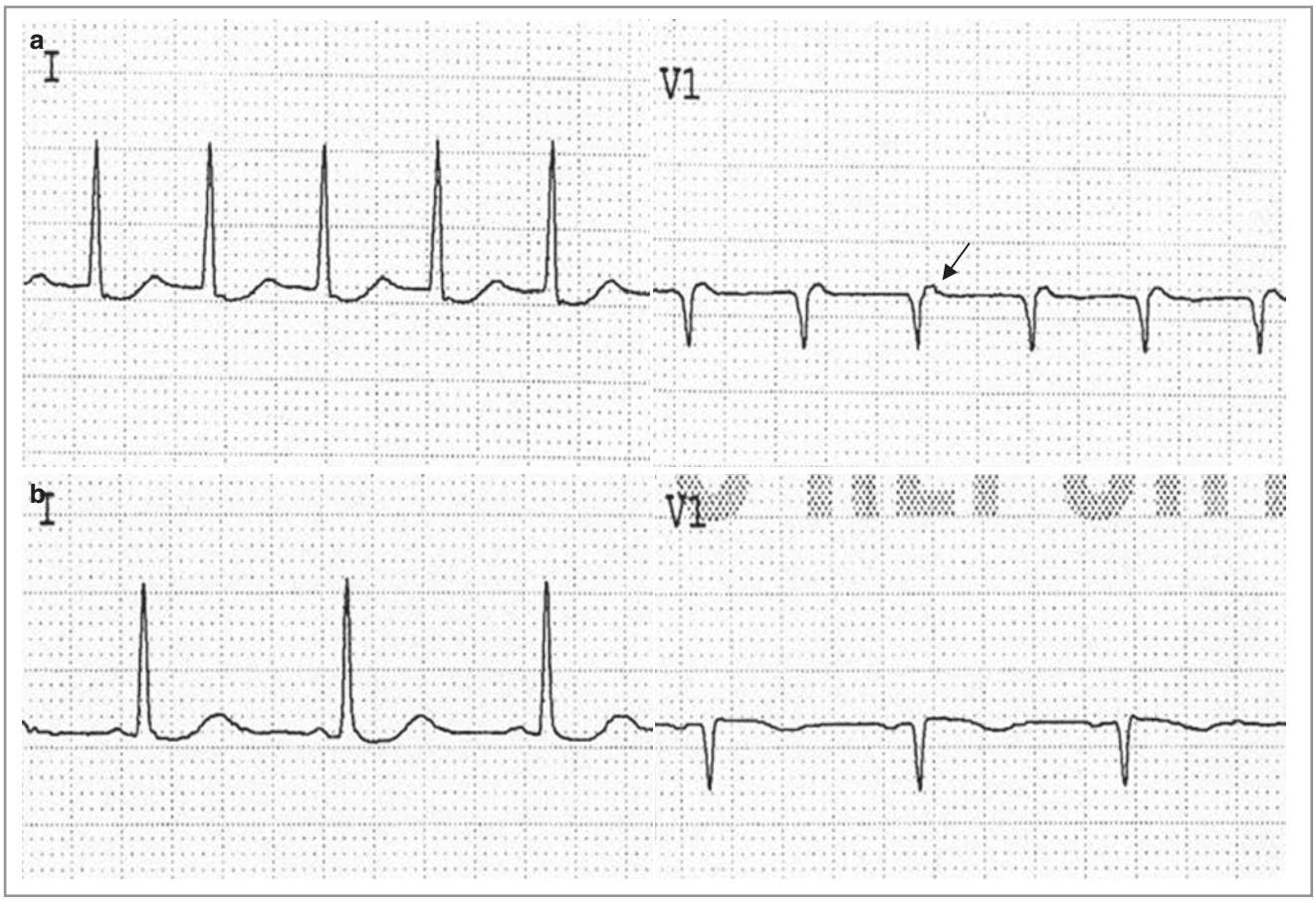


FIGURE 30-41

(**a**) Atrioventricular nodal reentrant tachycardia *(supraventricular tachycardia)*. Retrograde P wave denoted by the arrow. Compare to (**b**) baseline ECG during normal sinus rhythm

L. **Atrioventricular reentrant tachycardia (AVRT)**

- A reentrant circuit that involves an accessory pathway as well as the normal AV node-His Purkinje system (macro re-entrant circuit).
- Regular rhythm with ventricular rates 140–240 bpm.

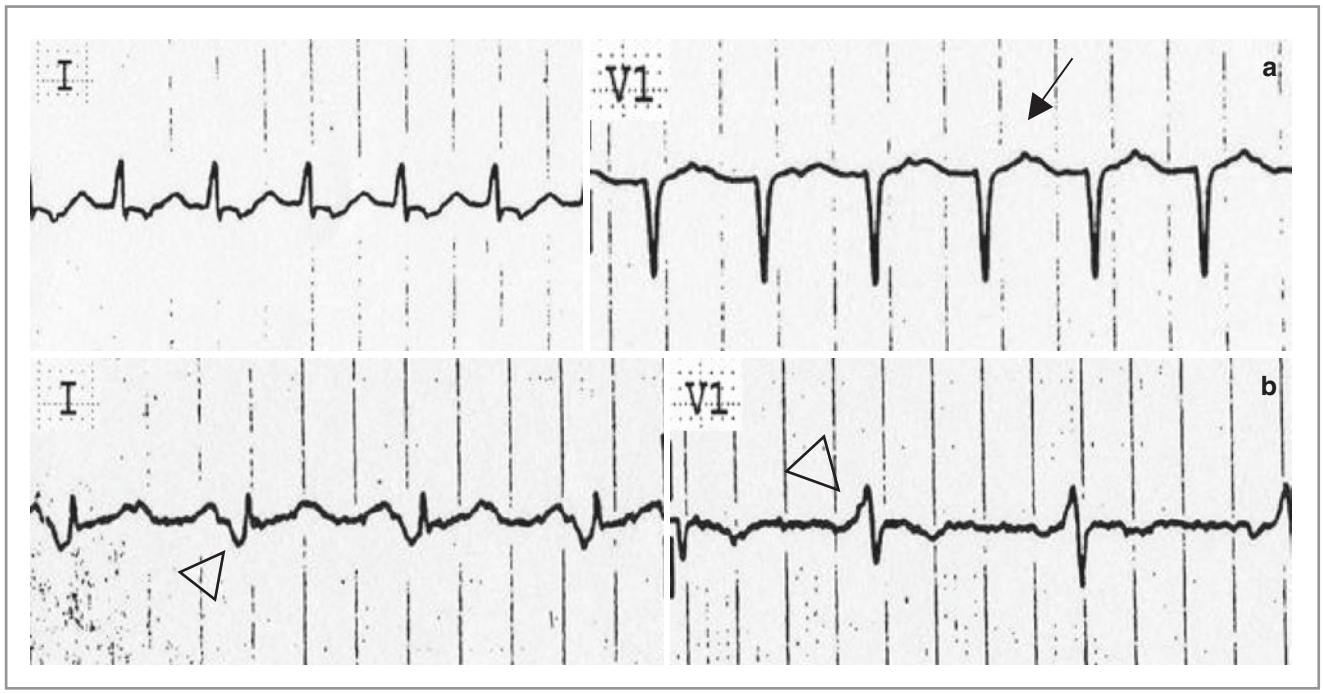


FIGURE 30-42

(**a**) Orthodromic atrioventricular reentrant tachycardia (*supraventricular tachycardia*). Retrograde P wave denoted by the arrow; (**b**) baseline ECG during normal sinus rhythm shows delta waves (arrowheads) indicating the presence of an accessory pathway

- **Orthodromic AVRT** (Fig. 30-42)—Narrow QRS complex with normal morphology due to antegrade conduction through the AV node-His Purkinje pathway and retrograde conduction via the accessory pathway.
- **Antidromic AVRT** (Fig. 30-43)—Similar QRS to the pre-excited QRS complex seen in sinus rhythm, but possibly wider (i.e. more maximally pre-excited) due to antegrade conduction through the accessory pathway with retrograde conduction via the His-Purkinje system. May be confused with ventricular tachycardia as QRS complex morphology is abnormal.

VENTRICULAR COMPLEXES AND RHYTHMS

A. **Premature ventricular complex (PVC,** Fig. 30-44)

- Also known as premature ventricular beat (PVB), ventricular premature complex (VPC), or ventricular premature beat (VPB).
- Early (premature) wide/abnormal QRS complex without a preceding P wave.
- P wave after QRS complex may or may not be seen. If a P wave is seen it may be retrograde (via VA conduction) or the on-time sinus P wave which is unrelated to the PVC (i.e. there is AV dissociation).
- Following a PVC, there is a full compensatory pause (i.e. the PP interval surrounding the PVC is twice the baseline PP interval, Fig. 30-44a).
- PVCs may be interpolated (i.e. there is no disruption of the surrounding sinus rhythm and no compensatory pause is present, Fig. 30-44b).
- As the most common mechanism is reentry there is usually a fixed relationship or fixed coupling interval between the preceding supraventricular complex and the PVC.
- **Unifocal PVCs**—Every PVC has the same morphology.
- **Multifocal PVCs**—Two or more different PVC morphologies.

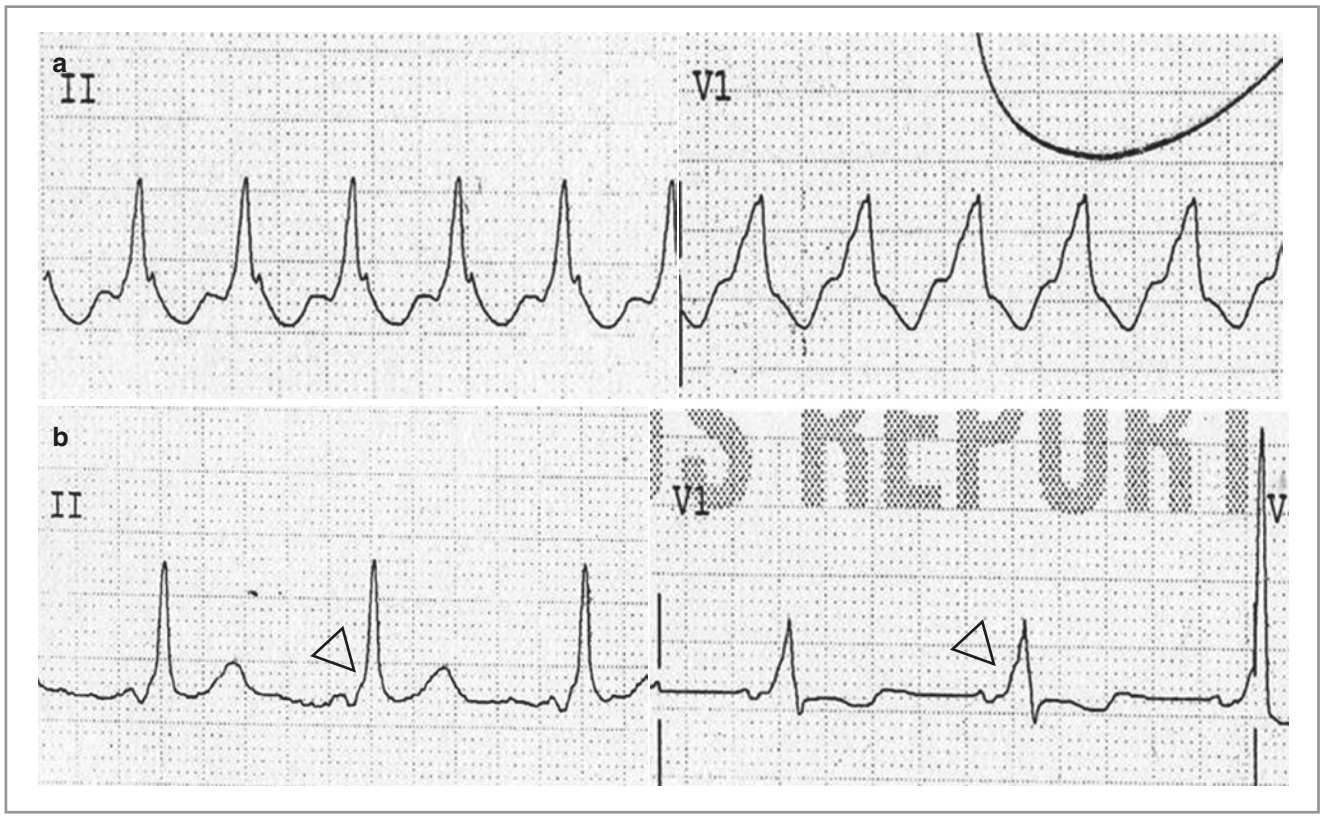


FIGURE 30-43

(**a**) Antidromic atrioventricular reentrant tachycardia (*supraventricular tachycardia*). The QRS complex is wide, aberrated, abnormal in morphology and maximally pre-excited; (**b**) baseline ECG during normal sinus rhythm shows delta waves (arrowheads) indicating the presence of an accessory pathway

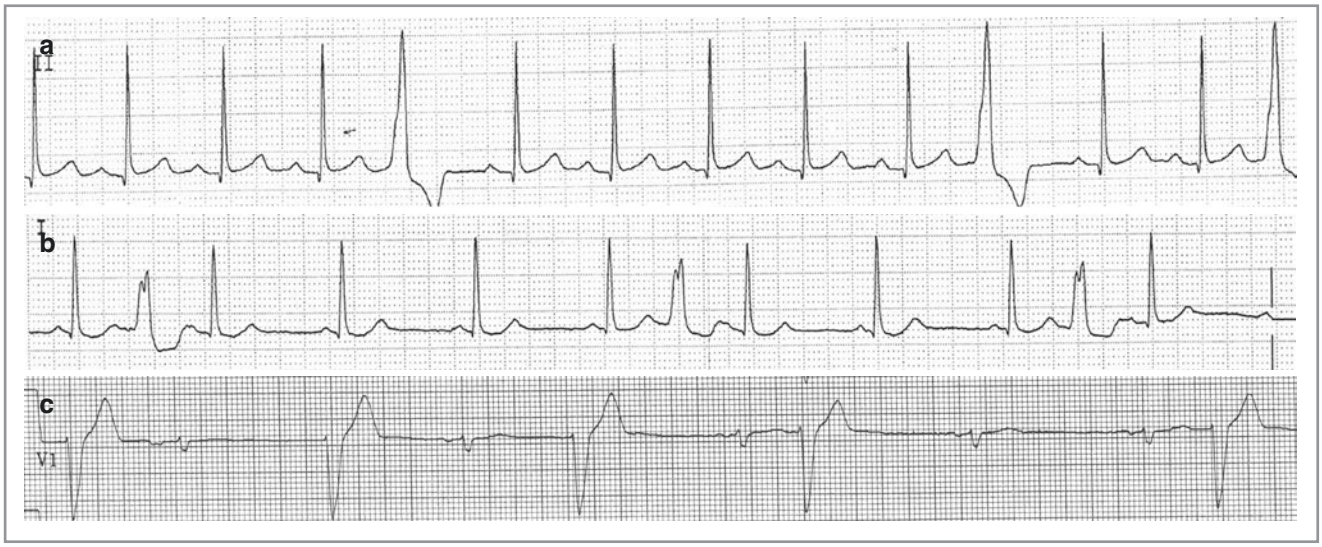


FIGURE 30-44

(**a**) Unifocal *ventricular premature complex(es)* with compensatory pauses; (**b**) unifocal interpolated PVCs; (**c**) *ventricular parasystole* as appreciated by the unifocal PVCs occurring at varying coupling intervals to the native QRS complexes (as compared to (**a**, **b**) where the coupling intervals are constant)

- **Ventricular bigeminy**—Every other QRS complex is a PVC.
- **Ventricular trigeminy**—Every third QRS complex is a PVC.
- Ventricular parasystole (Fig. 30-44c)
  - An ectopic focus that fires independent of the basic sinus rhythm (i.e. entrance block) with ventricular depolarization only when the myocardium is able to respond (i.e. exit block).
  - Unifocal PVCs with varying coupling intervals to the preceding QRS complexes.
  - Interectopic intervals are a multiple of the shortest interval noted between PVCs.

B. **Ventricular rhythms**

- Wide QRS complexes (≥0.12 s) that have an abnormal morphology (i.e. not a typical right or left bundle branch block) due to direct myocardial activation.
- P waves may be absent, unrelated to the QRS complex (i.e. AV dissociation with atrial rate slower than ventricular rate) or conducted in a retrograde fashion (i.e. VA conduction).
- Fusion or captured (Dressler) beats may be seen (indicative of AV dissociation).
- Ventricular rhythm—Rate < 60 bpm.
- Accelerated idioventricular rhythm (AIVR or slow VT; Fig. 30-45)—Rate 60–100 bpm.
- Ventricular tachycardia (VT)—Rate > 100 bpm (ventricular flutter for rate > 260 bpm).
  - **Monomorphic**—Single QRS morphology.
  - **Polymorphic**—Variability in QRS morphology and axis.
  - **Non-sustained (NSVT)**—3 or more sequential ventricular complexes lasting less than 30 s (or self teminating). NSVT may be monomorphic (Fig. 30-46a) or polymorphic (Fig. 30-46b).
  - **Sustained VT**—Sequential ventricular complexes lasting more than 30 s or terminated within 30 s because of hemodynamic instability (Fig. 30-47).
  - **Torsades de pointes** (Fig. 30-48)—Polymorphic VT associated with prolongation of the QT interval of the sinus complex.
- **Ventricular fibrillation (VF;** Fig. 30-49)—Absence of organized QRS complexes with fibrillatory waves that are irregular in morphology, interval, and amplitude. Fibrillatory waves are coarse at the onset of ventricular fibrillation and become finer as fibrillation duration is longer.

RATE-RELATED ABERRATION (FIG. 30-50A–D)

- Widening of the QRS complex that may occur at faster rates due to underlying conduction system disease or a decrease in conduction velocity (e.g. class I antiarrhythmic medications, tricyclic antidepressants, or hyperkalemia).
- Ashman's phenomenon (Fig. 30-50e)
  - Normally the His-Purkinje system refractoriness changes with heart rate—prolonged refractory period with slower heart rates and vice versa. This accounts for the relationship between QT interval and heart rate.

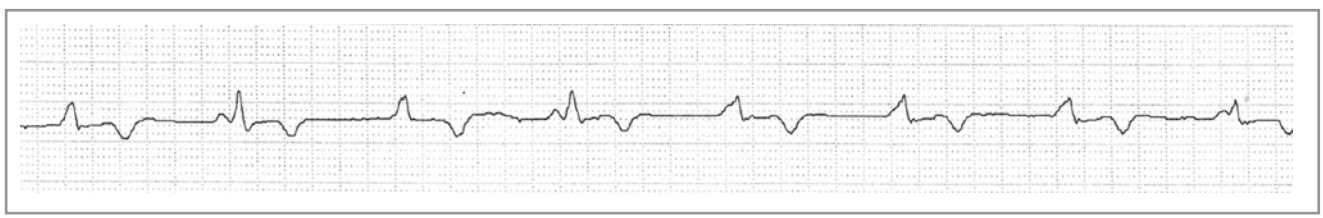


FIGURE 30-45

Accelerated idioventricular rhythm

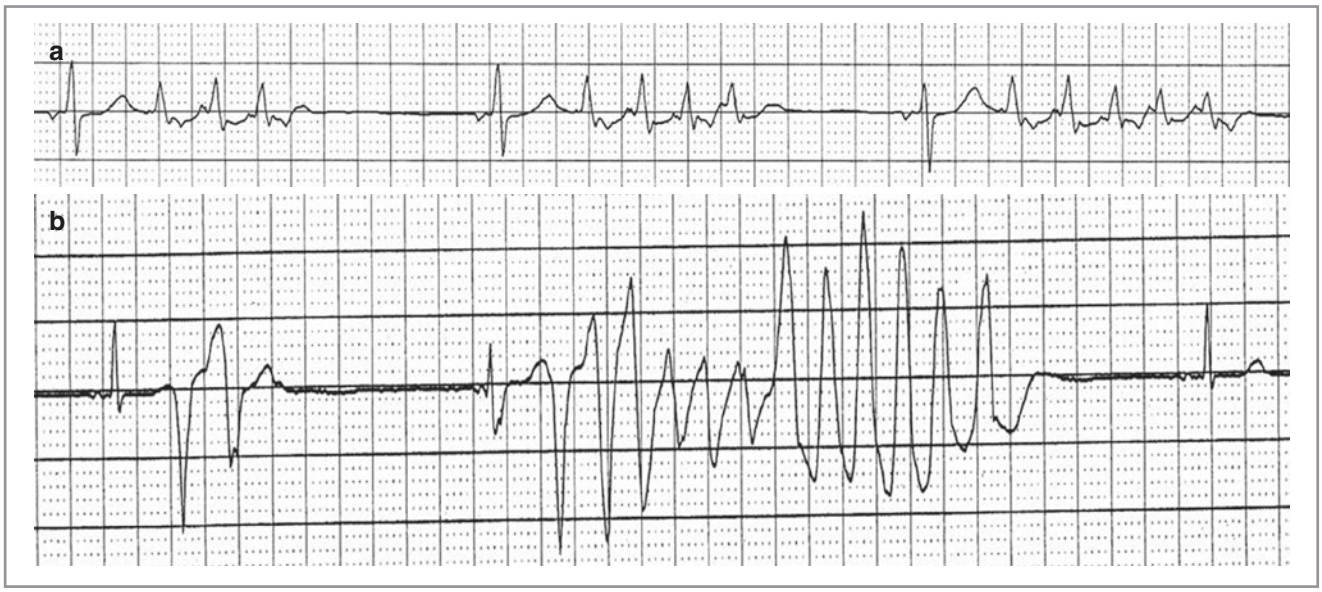


FIGURE 30-46

(**a**) Non-sustained monomorphic *ventricular tachycardia (3 or more consecutive complexes lasting less than 30 sec)* and (**b**) non-sustained polymorphic *ventricular tachycardia (3 or more consecutive complexes lasting less than 30 sec)*. Note that in the presence of a normal QTc interval this is not torsades de pointes

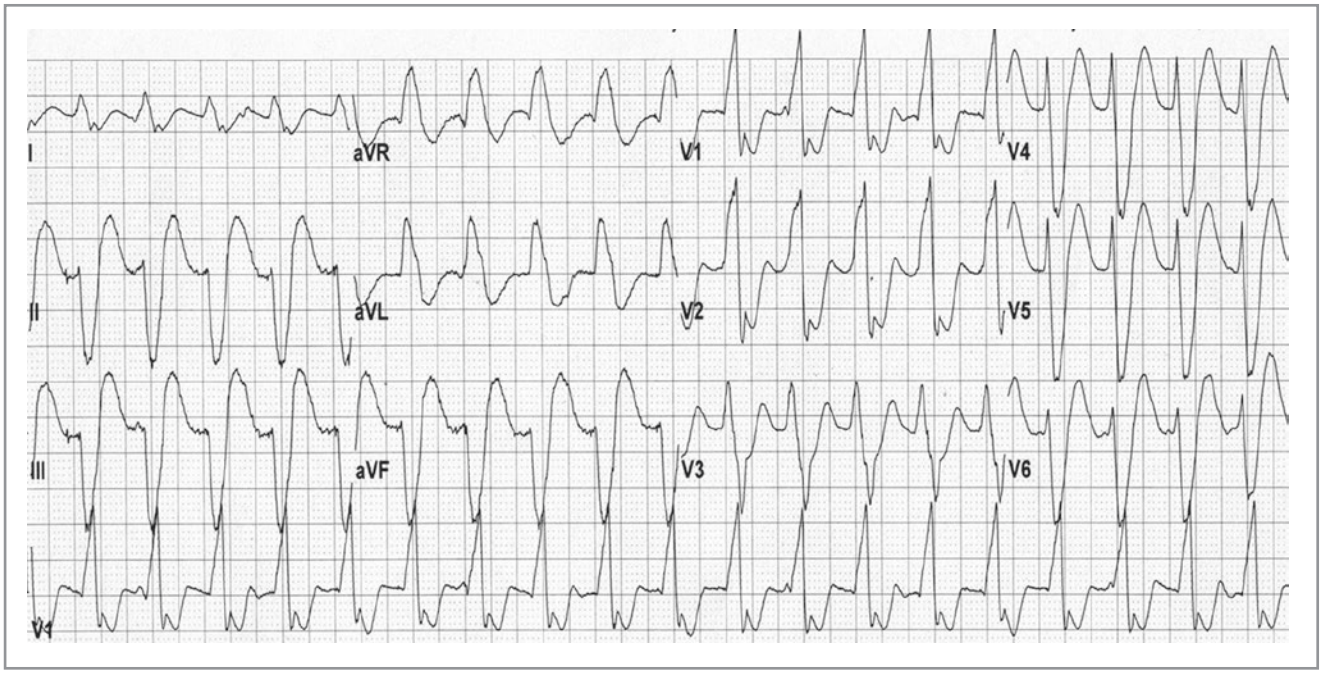


FIGURE 30-47

Sustained monomorphic *ventricular tachycardia (3 or more consecutive complexes lastin more than 30 sec)*

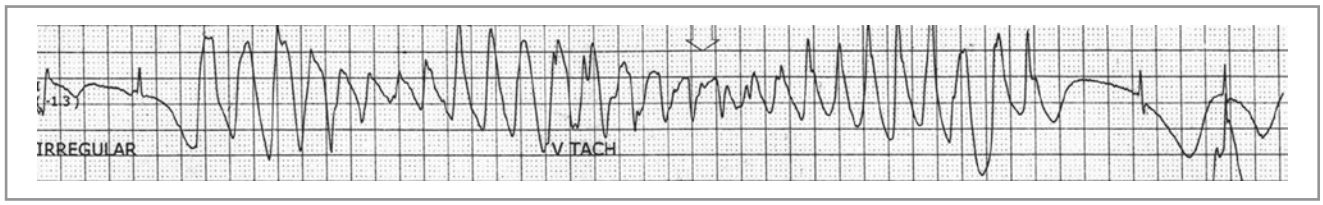


FIGURE 30-48

Torsades de pointes, a polymorphic ventricular tachycardia in the setting of a prolonged QTc interval

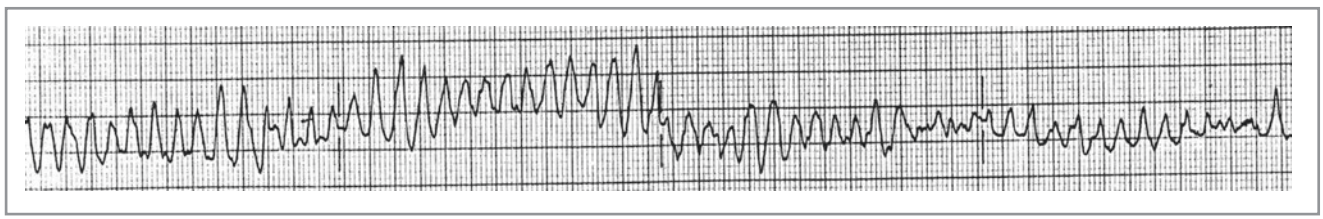


FIGURE 30-49

Ventricular fibrillation

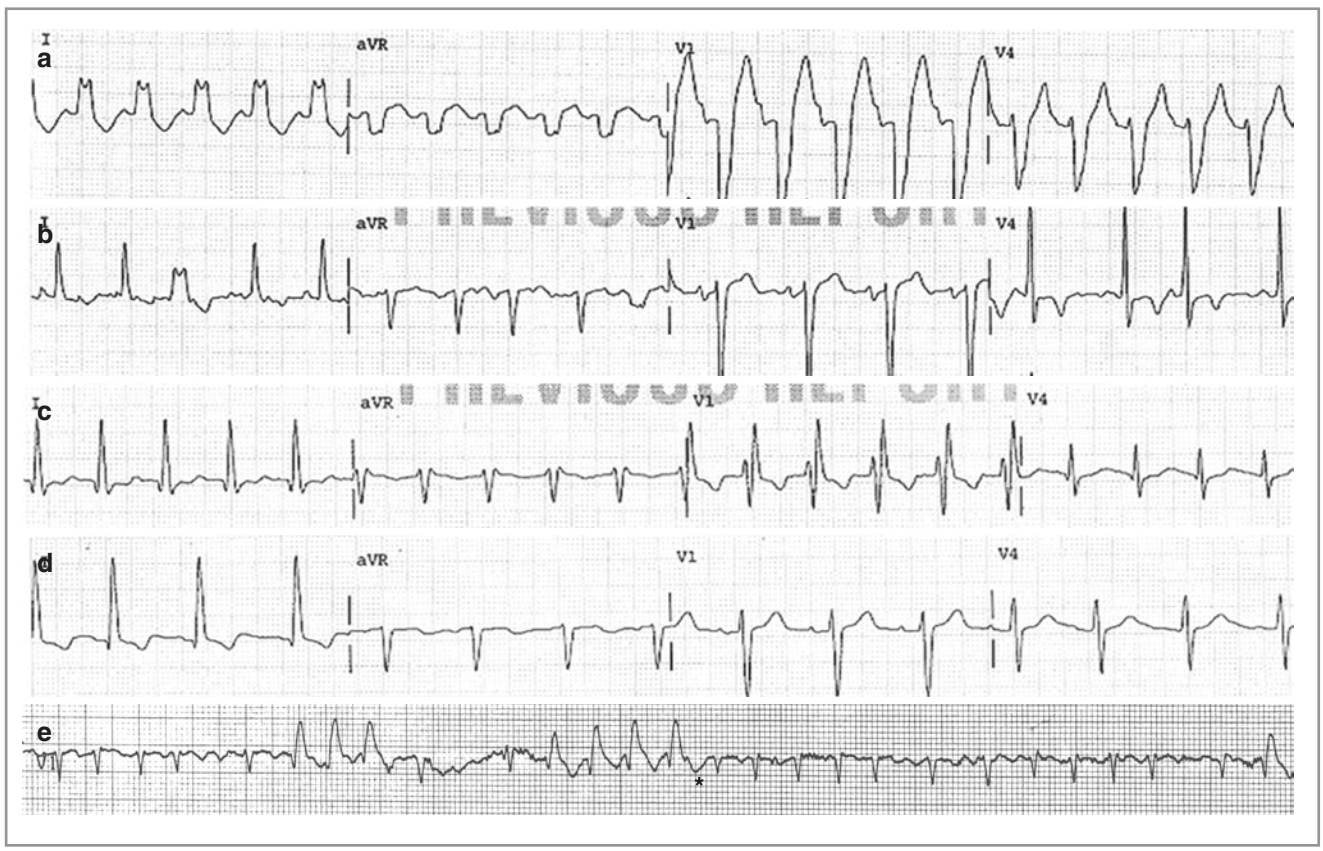


FIGURE 30-50

Aberrant conduction (including rate-related). (**a**, **b**) Rate related LBBB. Abrupt onset of aberration occurs above a certain heart rate threshold. Compare the faster heart rate in (**a**) to that of the same patient in (**b**); (**c**, **d**) rate related RBBB. Abrupt onset of aberration occurs above a certain heart rate threshold. Compare the faster heart rate in (**c**) to that of the same patient in (**d**); (**e**) Ashman's phenomenon (i.e. aberration associated with a preceding "long-short" RR cycle). With a sudden increase in heart rate (common in atrial fibrillation shown here), aberrancy occurs for just a few beats (usually a RBBB pattern) before the His-Purkinje refractoriness adapts to the fast heart rate. Note the complexes following the RBBB beats marked by the * occur at the same R-R interval but are no longer aberrated. This feature distinguishes Ashman's phenomenon from rate related aberration (in which **all** beats above a threshold heart rate are aberrated)

- With a sudden change in heart rate from slow to fast (i.e. a "long-short" RR cycle) refractoriness of the His-Purkinje does not adapt immediately resulting in aberration of one or more QRS complexes.
- Typically, this aberration has a RBBB morphology.

CLINICAL DISORDERS

A. **Antiarrhythmic drugs** (Table 30-2)

■ Antiarrhythmic drug effect

- Class IA and IC antiarrhythmic drugs **slow conduction** and therefore prolong the QRS complex duration. This prolongation is greater with faster heart rates (i.e. use dependence, Fig. 30-51).
- Class IA and class III antiarrhythmic drugs **prolong repolarization** and therefore elongate the QT and QTc intervals.
- Class IB antiarrhythmic drugs also slow conduction but only minimally and hence no change in QRS complex duration is usually seen, Class II antiarrhythmic drugs or beta blockers and class IV antiarrhythmic drugs or calcium channel blockers primarily effect sinus and AV nodes.

TABLE 30-2

DRUG EFFECT AND TOXICITY OF ANTIARRHYTHMICS AND DIGITALIS

DRUG	DRUG EFFECT	DRUG TOXICITY
Antiarrhythmics	■ ↑ QRS interval (IA, IC) ■ ↑ QT interval (IA, III) Sinus slowing or arrest ■ ↑ PR interval or AV block (class II, IV)	■ Marked QRS widening (IA, IC) ■ Torsades de pointes (IA, III) ■ Proarrhythmia (IA, IB, IC, III) ■ Sinus bradycardia, sinus arrest and AV block (class II or IV)
Digitalis	■ ST segment scooping, sagging or hammock-like ■ ↓ QT interval ■ ↑ PR interval	■ Sinus bradycardia ■ Atrial tachycardia with AV block ■ Accelerated junctional rhythm ■ Regularized AF ■ Bidirectional junctional or ventricular tachycardia ■ VT and/or VF

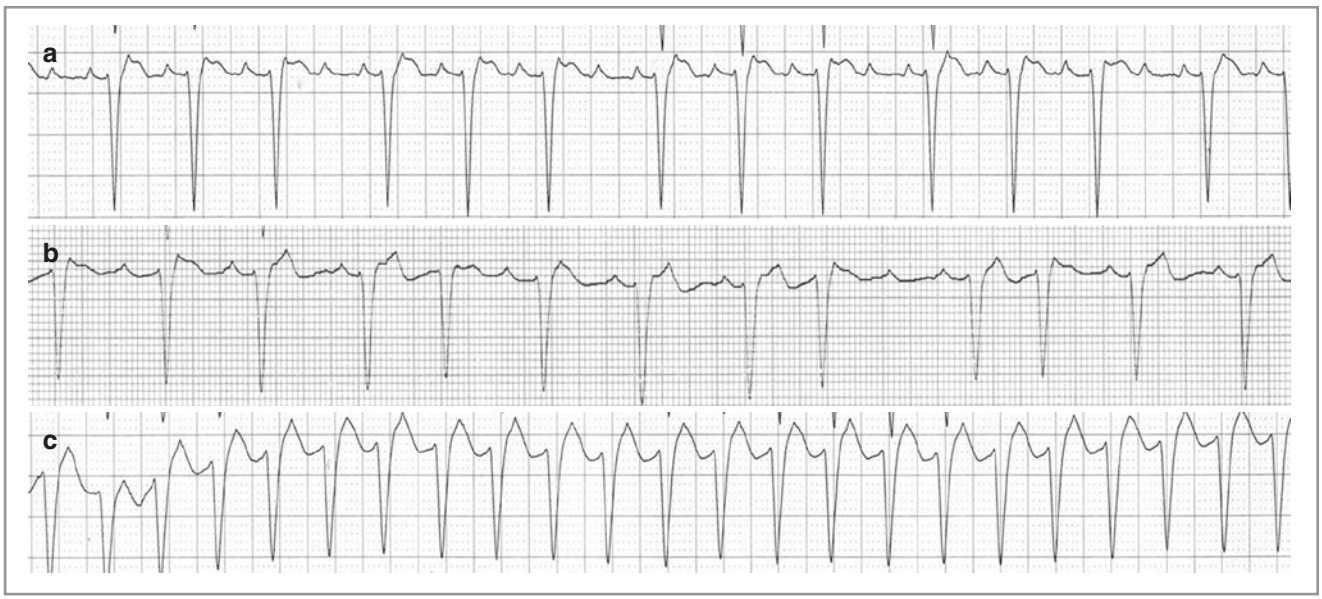


FIGURE 30-51

Use dependent effects of class I antiarrhythmic drugs. (**a**) Baseline rhythm is atrial flutter with variable AV conduction (atrial rate is approximately 220 bpm); (**b**) after initiation of a class I antiarrhythmic, the atrial rate has slowed to 150 bpm, but AV conduction is still variable; (**c**) now there is 1:1 AV conduction, but the QRS has widened due to use dependence

- Antiarrhythmic drug toxicity
  - Significant QRS complex widening (IA and IC)
  - Marked QT interval prolongation with torsades de pointes (IA and III)
  - Proarrhythmia (IA, IB, IC and III)
  - Sinus bradycardia, sinus arrest and varying degrees of AV block (class II drugs or beta blockers and class IV antiarrhythmia drugs or calcium channel blocker)

B. **Digitalis** (Table 30-2)

- **Digitalis effect** (Fig. 30-52a)—Seen in patients taking digoxin at therapeutic and even subtherapeutic levels.
  - Sagging, scooping or hammock-like depression of the ST segment with a normal J point
  - Shortened QT interval
  - Prolonged PR interval
- **Digitalis toxicity**—Associated with digoxin excess. May be exacerbated by hypokalemia, hypomagnesemia or hypocalcemia. Virtually any cardiac arrhythmia or conduction abnormality can occur, but typical findings include:
  - Sinus bradycardia
  - Atrial tachycardia with AV block (Fig. 30-35c)
  - Accelerated junctional rhythm (Fig. 30-52b)
  - Regularization of atrial fibrillation (i.e. atrial fibrillation with complete heart block and a junctional escape rhythm)
  - Bidirectional junctional (alternating bundle conduction) or what has been reported to be bidirectional ventricular tachycardia (Fig. 30-52c)
  - Ventricular tachycardia or ventricular fibrillation

C. **Hyperkalemia**

- Initial changes are most commonly tall, peaked, **symmetric** T waves (upstroke and downstroke of T wave the rate).
- Prolongation of the PR interval with eventual atrial asystole (Fig. 30-53a).
- QRS interval prolongation (QRS duration ≥0.24 s is pathognomonic for hyperkalemia, Fig. 30-53b).
- "Sine wave" pattern in the most severe forms of hyperkalemia.

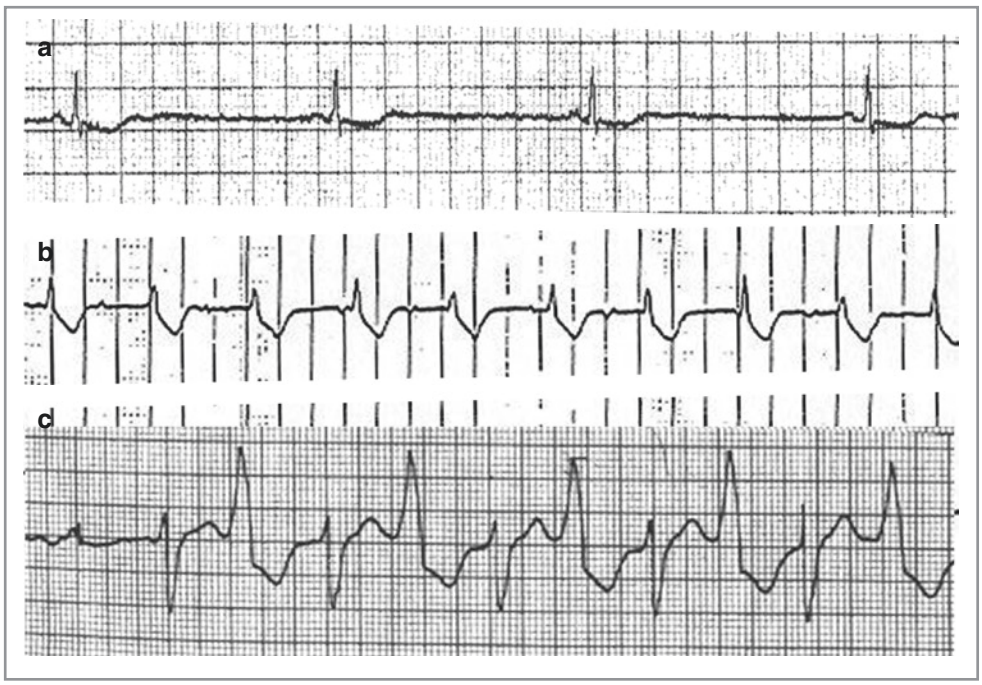


FIGURE 30-52

(**a**) Digitalis effect with "hammock-like" ST segments; (**b**) *digitalis toxicity* manifested by *atrial tachycardia* with *AV block, 3°* and an *AV junctional tachycardia*; (**c**) *digitalis toxicity* manifested by bidirectional ventricular tachycardia

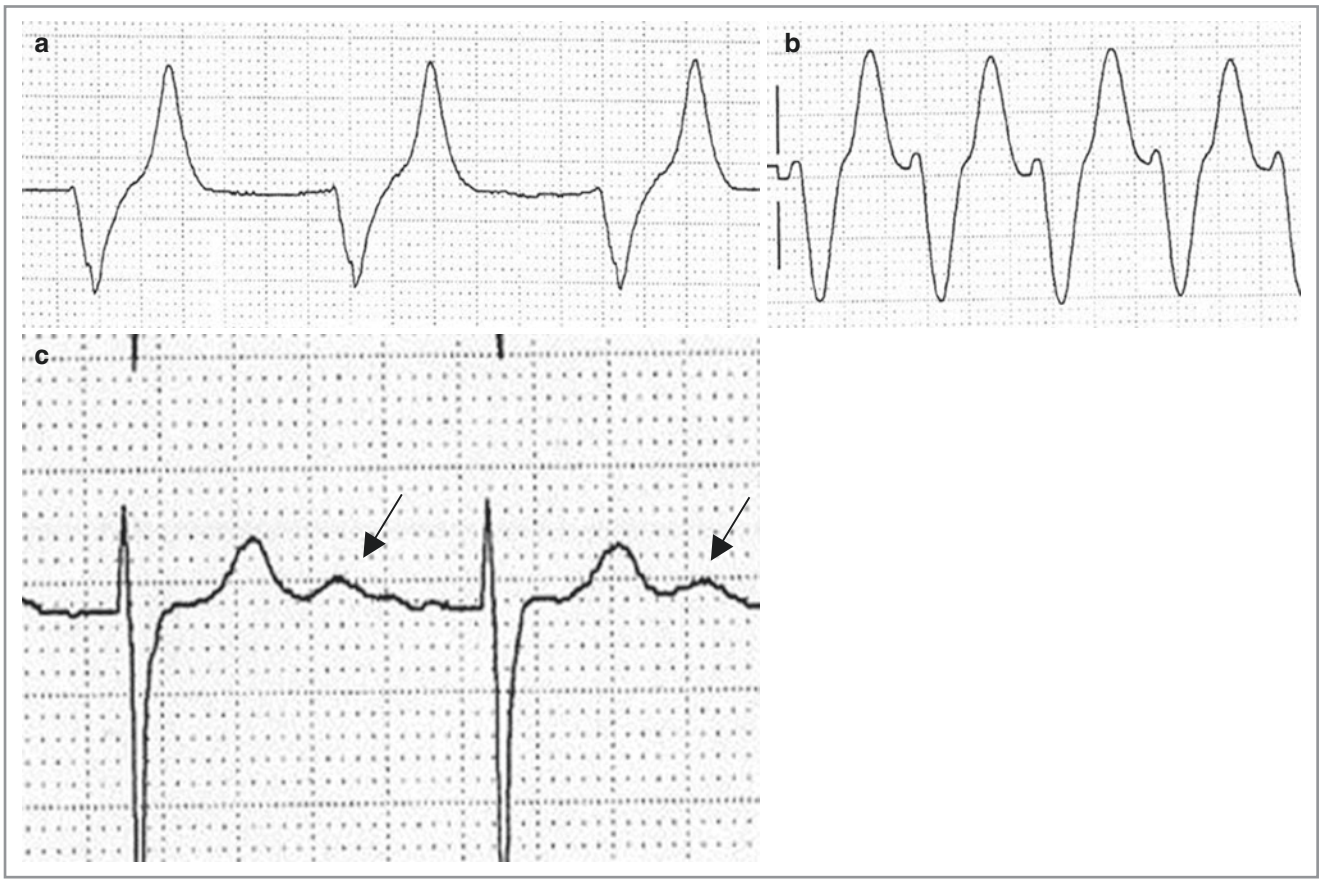


FIGURE 30-53

(**a**, **b**) *Hyperkalemia* punctuated by tall, peaked and **symmetric** T waves (*ST and/or T wave abnormalities suggesting electrolyte disturbances*), loss of P waves (atrial asystole) and a prolonged QRS interval. Note that a QRS duration ≥ 0.24 s is pathognomonic for hyperkalemia (as visualized in (**b**)); (**c**) *hypokalemia* with *prominent U waves*

D. **Hypokalemia**

- Characterized by ST segment depression with T wave flattening.
- Typically associated with prominent U waves (Fig. 30-53c).
- QT prolongation may also be seen.

E. **Hypercalcemia (and hypermagnesemia,** Fig. 30-4d)

- Shortening of the QT interval (typified by a short isoelectric ST segment with normal T wave duration).
- PR prolongation may also be present.

F. **Hypocalcemia (and hypomagnesemia,** Fig. 30-4a)

- Lengthening of the QT interval (typified by a long, isoelectric ST segment with normal T wave duration).

G. **Atrial septal defect (ASD)**

- **Ostium secundum ASD**—Right axis deviation, right atrial abnormality and RVH (when left to right shunting is present).
- **Ostium primum ASD** (Fig. 30-54)—Congenital LAFB, RVH and rSR' in lead V1. The axis is typically leftward (due to the LAFB), but may be indeterminate due to contributions from RVH.
- First degree AV block may be seen in either ASD, but more commonly in ostium primum.

H. **Dextrocardia** (Fig. 30-55)

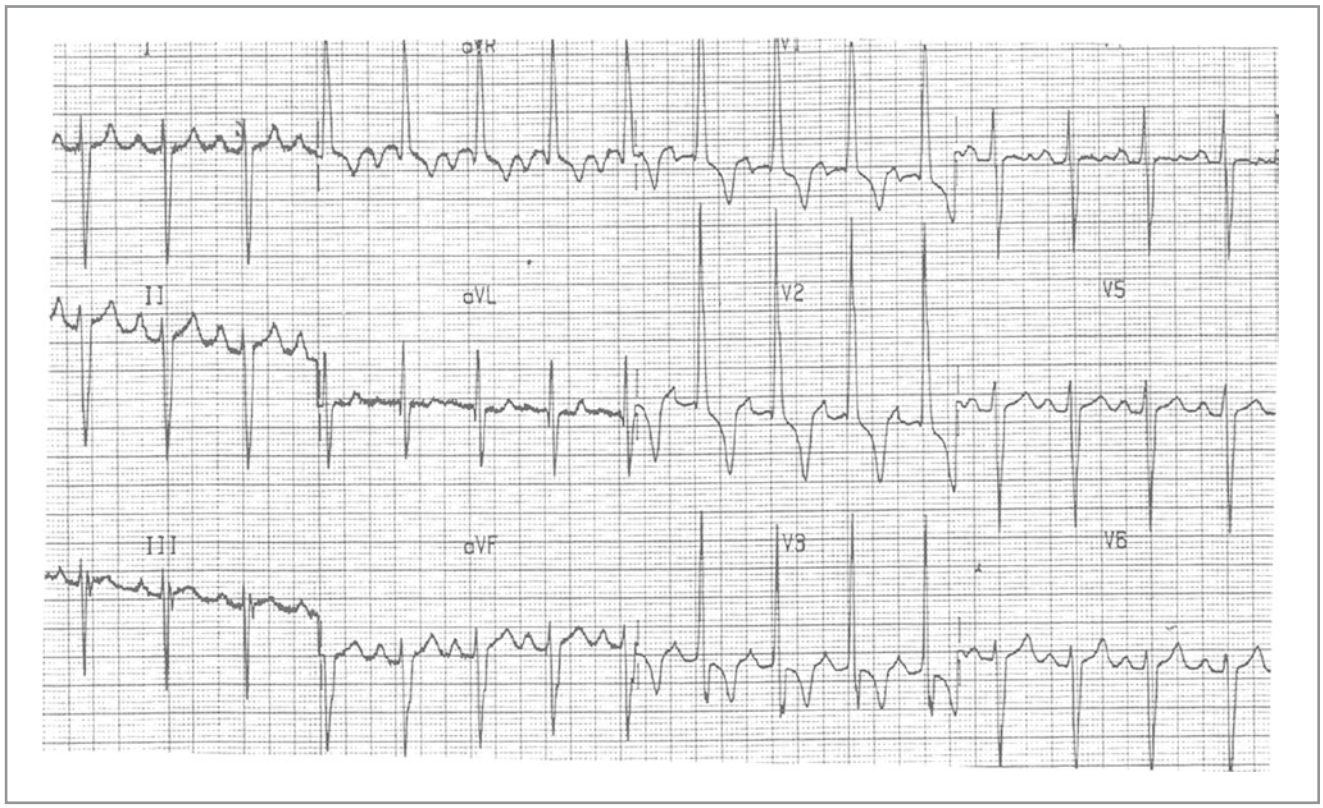


FIGURE 30-54

Ostium primum ASD. Note the indeterminate axis due to congenital LAFB and right axis shift in the setting of RVH

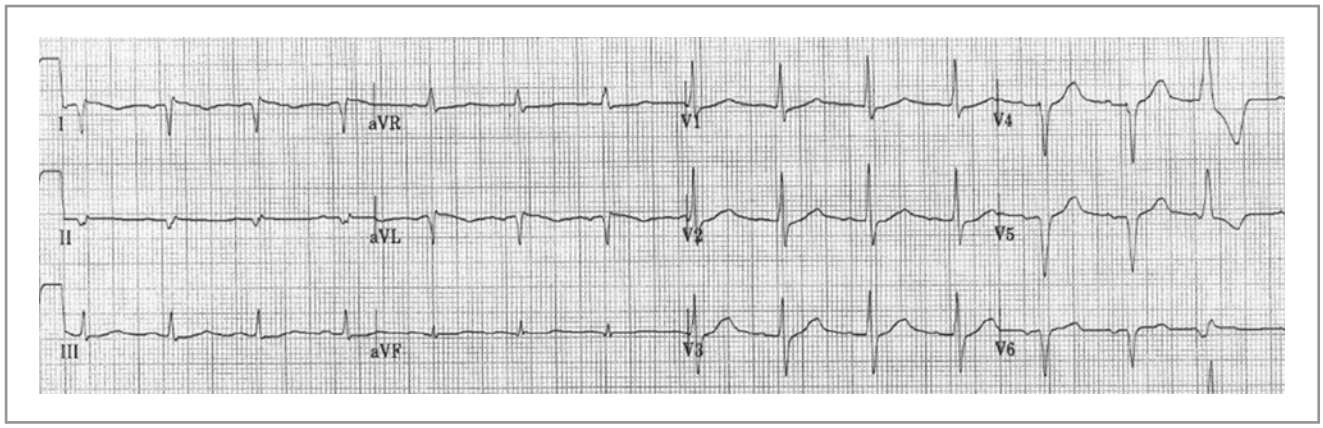


FIGURE 30-55

Dextrocardia, mirror image

- Appears similar to right-left arm lead switch wherein P, QRS and T waves are all negative in lead I, but positive in lead aVR.
- The distinguishing feature of dextrocardia **is reverse R wave progression in leads V1–V6**.

I. **Chronic lung disease**

- Diffuse low voltage and poor R wave progression across precordium (i.e. clockwise rotation).

- May also cause RVH, right axis deviation and right atrial abnormality when associated with cor pulmonale.

J. **Acute cor pulmonale including pulmonary embolus** (Fig. 30-56)

- S1Q3T3 (S wave in lead I, Q wave in lead III and inverted T wave in lead III; the McGinn-White sign). Generally represents a right axis shift.
- IVCD (i.e. incomplete right bundle branch block) or a right bundle branch block in the setting of increased RV pressure.
- May see concomitant right axis deviation with right atrial abnormality, in addition to downsloping ST-T wave changes in leads V1–V3.

K. **Pericardial effusion** (Fig. 30-57)

- Low voltages
- **Electrical alternans**—Beat to beat changes in the amplitude of the QRS complex during a regular rhythm. Often co-exists with T wave alternans (beat to beat changes in the amplitude of the T wave), whereas P wave alternans (beat to beat changes in the amplitude of the P wave) is rarely seen but is only seen with pericardial effusion or tamponade. Electrical and T wave alternans. Also occurs with:
  - Rapid and regular supraventricular tachycardias (e.g. atrial tachycardia, atrial flutter, AVRT, ANRT)
  - Cardiomyopathy
  - Decompensate congestive heart failure
  - Acute MI
  - VT (uncommonly)

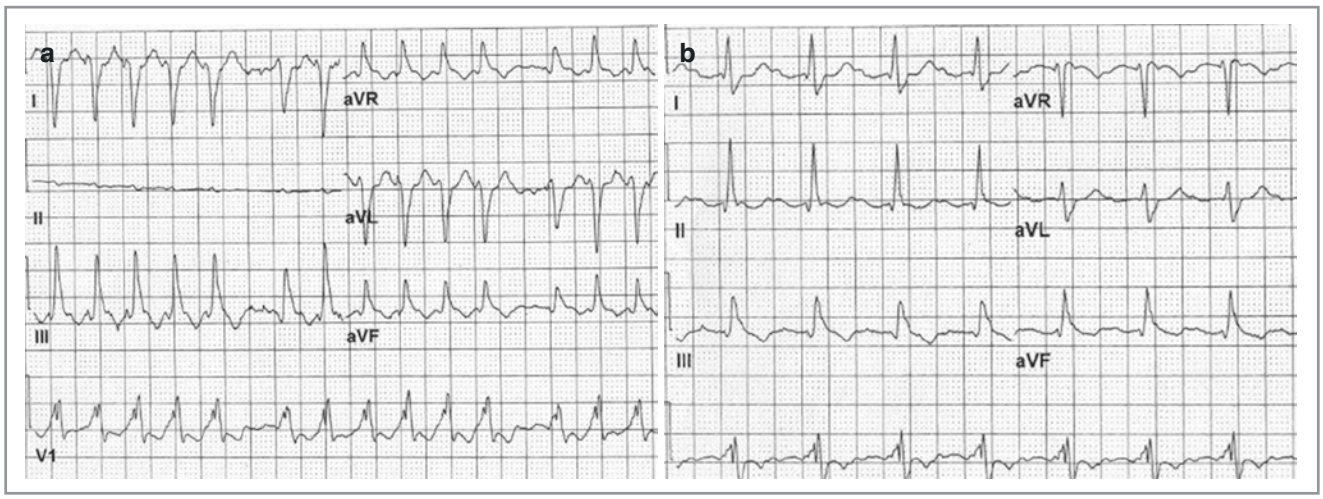


FIGURE 30-56

(**a**) *Acute cor pulmonale including pulmonary embolus*, compared to (**b**) baseline ECG

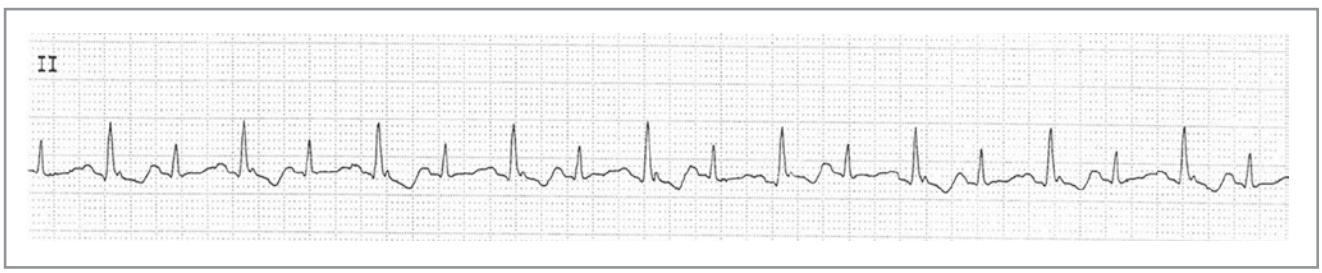


FIGURE 30-57

Pericardial effusion. Note the presence of *electrical alternans*, P wave alternans and T wave alternans.

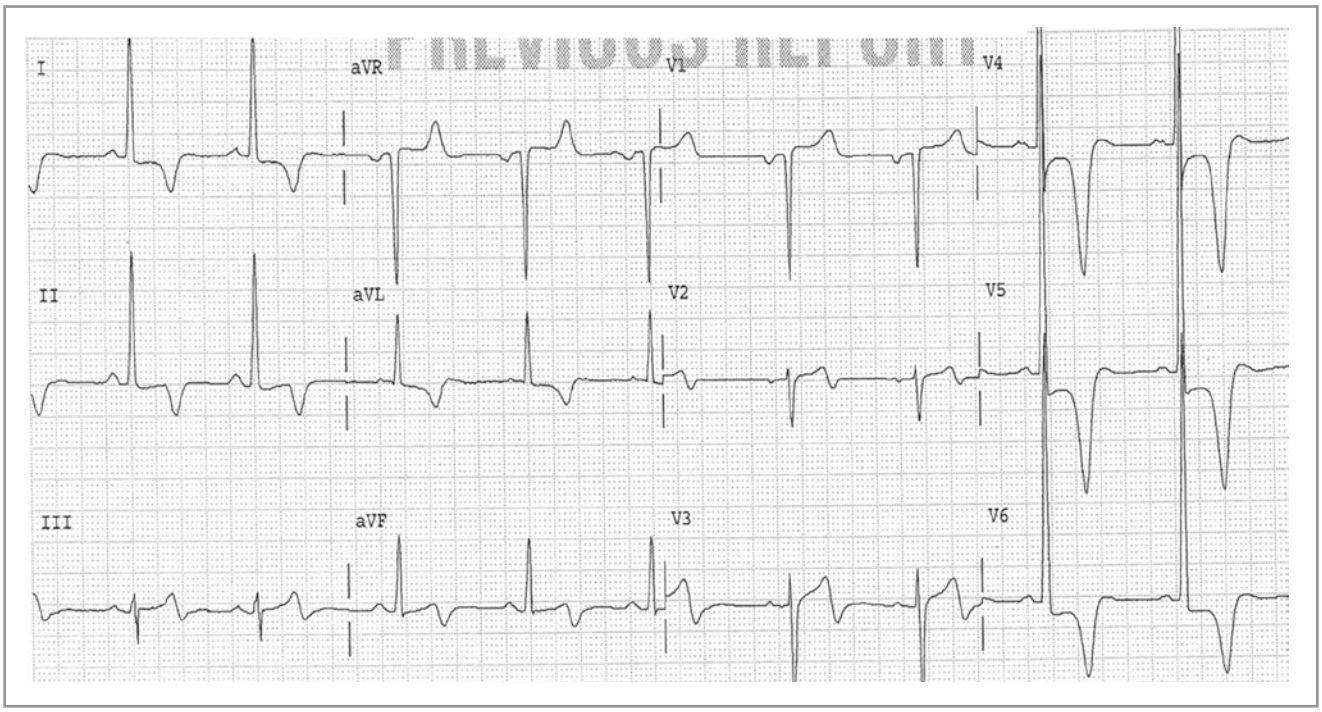


FIGURE 30-58

Hypertrophic cardiomyopathy

L. **Hypertrophic cardiomyopathy** (Fig. 30-58)

- Prominent Q waves in the inferior, anterior and lateral leads (II, III, aVF, I, aVL, V4–V6) and prominent and tall R wave in V1 due to septal depolarization of the hypertrophied myocardium.
- Usually significant LVH with associated ST-T wave changes, in addition to left atrial abnormality
- Occasionally with left axis deviation or right atrial abnormality.

M. **Myxedema**

- Diffusely low voltages with flattened T waves (due to myxedematous changes of the myocardium).
- Frequently associated with pericardial effusion and its associated findings (see "Pericardial effusion").
- Sinus bradycardia and prolonged PR interval are also seen.

N. **Hypothermia**

- Results in elevation of the J point, known as an Osborne or J wave (Fig. 30-59).

O. **Sick sinus syndrome**

- Sinoatrial node dysfunction in the presence or absence of associated AV nodal conduction abnormalities. This includes:
  - **Tachycardia-bradycardia ("Tachy-brady") syndrome**—Abrupt termination of an atrial tachyarrhythmia with a long offset pause, after the pause may have a sinus or a junctional escape rhythm or a ventricular escape rhythm (Fig. 30-60).
  - **Chronotropic incompetence**—Failure to increase the sinus rate with sympathetic stimulation.

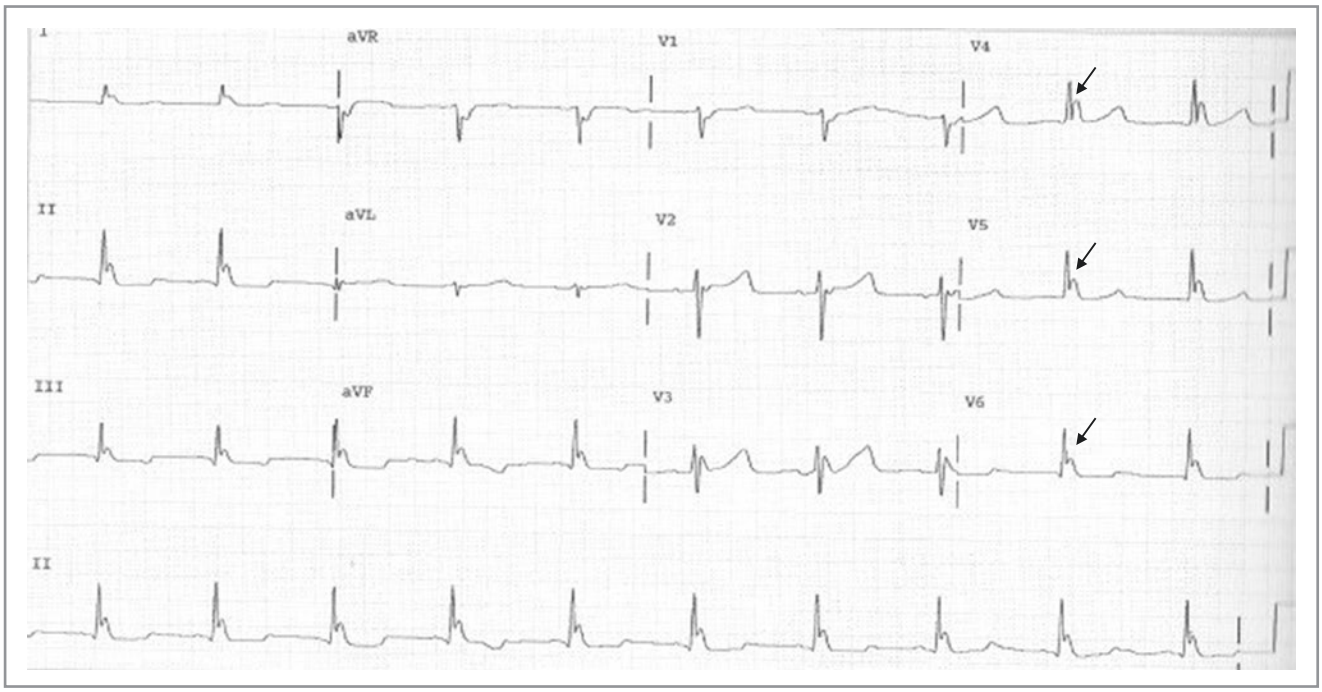


FIGURE 30-59

Osborne waves in *hypothermia*. The arrows denote the Osborne (or J) waves

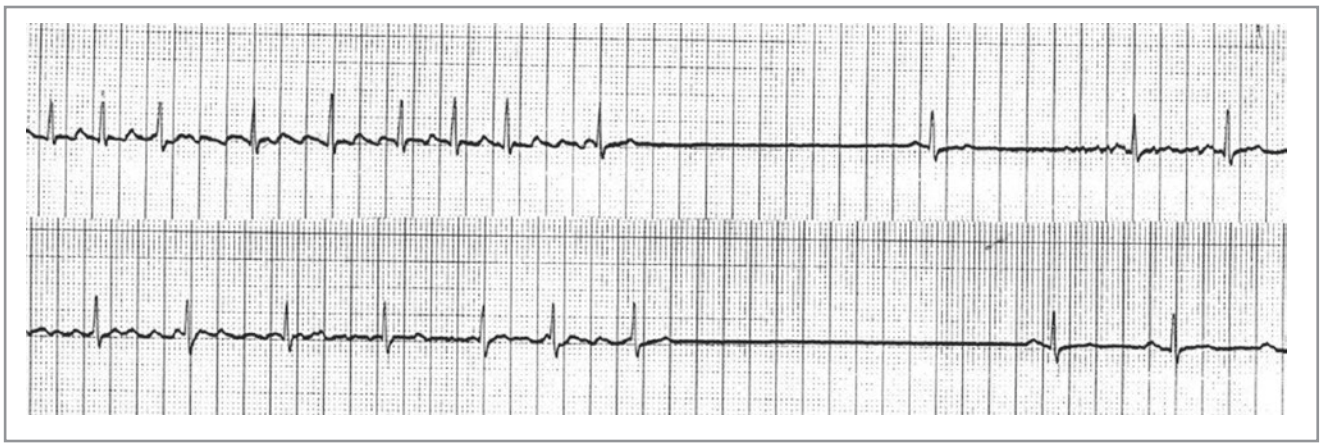


FIGURE 30-60

Sick sinus syndrome characterized by *atrial fibrillation* and a prolonged *sinus pause or arrest*

- **Bradycardia-tachycardia syndrome**—Profound bradycardia with an escape atrial tachyarrhythmia.
- Prolonged offset pause after a PAC.
- Chronic atrial fibrillation with a slow ventricular response in the absence of AV nodal blocking agents.

P. **Brugada pattern**

■ Results from a repolarization abnormality, creating an abnormality of the J point.

- **Type 1**—J point elevation in leads V1 and V2 with a slow descent of the ST segment to a negative T wave (Fig. 30-61a).

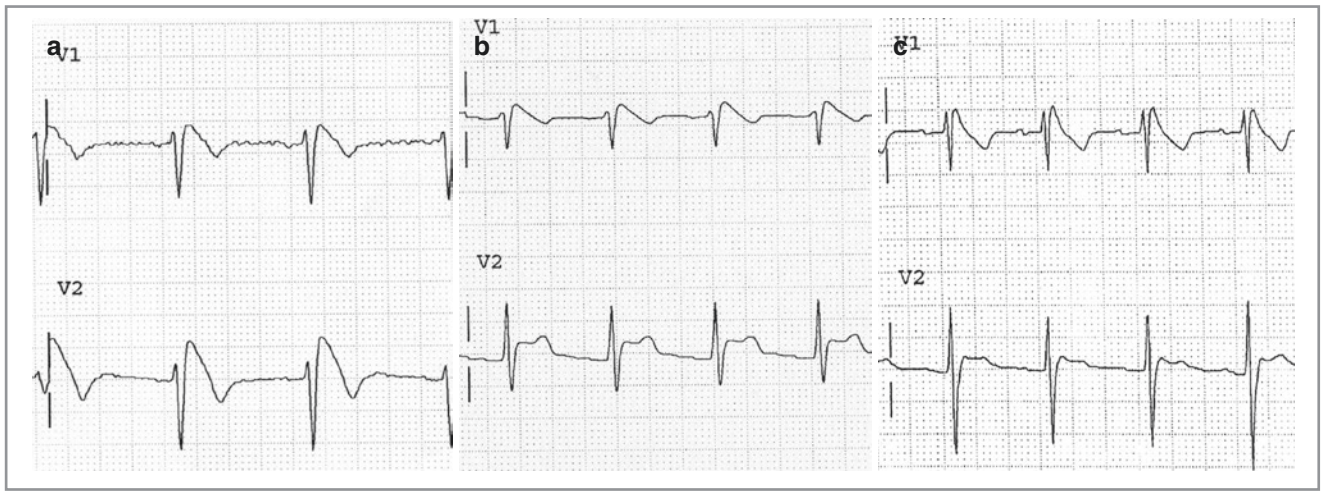


FIGURE 30-61

Brugada syndrome—(**a**) type 1, (**b**) type 2 and (**c**) type 3

- **Type 2**—J point elevation in lead V1 with a slow descent of the ST segment to a negative T wave. Lead V2 has J point and ST segment elevation that appear notched, termed a "saddle back" appearance (Fig. 30-61b).
- **Type 3**—J point elevation in lead V1 with a slow descent of the ST segment to a negative T wave. Lead V2 has J point elevation and the ST segment appears notched, however the latter is isoelectric and not elevated (Fig. 30-61c).

ECG'S

■ **Answers as listed on the official answers options list are *italicized* in the ECG descriptions**.

ECG's Quick List

1. Normal ECG
2. LAFB and LPFB
3. Low voltage
4. QT interval
5. Juvenile T waves
6. Hyperacute T waves
7. Acute subarachnoid bleed
8. ST segment depression
9. Pacemakers: normal atrial and ventricular pacing
10. Pacemakers: normal biventricular pacing
11. Pacemaker malfunction
12. Left atrial abnormality
13. Right atrial abnormality
14. LVH
15. RVH
16. Biventricular hypertrophy
17. Stages of acute MI
18. Inferior and posterior acute MI
19. Chronic MI
20. Acute pericarditis
21. Sinus arrest and sinoatrial exit block
22. 1° AV block

23. 2° AV block—Wenckebach
24. 2° AV block—Mobitz type II
25. 2:1 AV block
26. Complete heart block with escape rhythms
27. RBBB
28. LBBB
29. IVCD
30. WPW and LGL
31. Atrial fibrillation with WPW
32. Sinus bradycardia, tachycardia and arrhythmia
33. Premature atrial complexes
34. Premature junctional complexes
35. Ectopic atrial rhythm and atrial tachycardia
36. Wandering atrial pacemaker and multifocal atrial tachycardia
37. Atrial flutter
38. Atrial fibrillation
39. Junctional rhythms
40. AVNRT—Pathophysiology
41. AVNRT
42. Orthodromic AVRT
43. Antidromic AVRT
44. Premature ventricular complexes and ventricular parasystole
45. AIVR
46. Non-sustained monomorphic and polymorphic VT
47. Sustained monomorphic VT
48. Torsades de pointes
49. Ventricular fibrillation
50. Rate-related aberrancy and Ashman's Phenomenon
51. Class I antiarrhythmic drug effect
52. Digitalis effect and toxicity
53. Hyper and hypokalemia
54. Ostium primum ASD
55. Dextrocardia
56. Cor pulmonale due to acute pulmonary embolism
57. Pericardial effusion
58. Hypertrophic cardiomyopathy
59. Hypothermia
60. Sick sinus syndrome
61. Brugada syndrome

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