

# 2.5.2A

## Cardiovascular Medical Devices: Heart Valves, Pacemakers and Defibrillators, Mechanical Circulatory Support, and Other Intracardiac Devices

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### Introduction

Cardiovascular disease continues to be the leading cause of mortality and morbidity in the Western world, resulting in over 800,000 (nearly one-third of) deaths in the United States each year. Moreover, as the leading cause of death globally, cardiovascular disease kills more than 17 million individuals per year, a number that is expected to grow to more than 23 million by 2030. The most important subtype is coronary heart disease accounting for more than 1 in 7 deaths, killing over 360,000 people a year in the United States. Additionally, over 25,000 persons per year in the United States succumb to valvular heart disease, of which 17,000 have aortic valve disease, a number which is expected to double by 2040 and triple by 2060 (Benjamin et al., 2019).

The good news is that the past several decades have witnessed a virtual explosion in the number and scope of innovative surgical and interventional diagnostic and therapeutic procedures for patients with cardiovascular diseases. Data from the National Center for Health Statistics and the American Heart Association indicate that approximately 8 million major cardiac and vascular operations are performed annually in the United States. Concurrent with and integral to the broad application of these surgical and interventional procedures is the use of various prostheses and medical devices composed of highly advanced biomaterials. Data from 2014 show 475,000 percutaneous

coronary interventions (almost all using endovascular bare-metal or drug-eluting stents), 371,000 coronary artery bypass graft procedures, 156,000 cardiac valve procedures, pacemakers, leads, and cardioverter-defibrillators (420,000), and use of many cardiac assist devices, vascular grafts, umbrellas, patches, and other devices (D'Agostino et al., 2018; Benjamin et al., 2019).

Thus cardiovascular prostheses and medical devices, and their constituent biomaterials, are of critical importance to the practices of interventional cardiologists and cardiac and vascular surgeons. The number and complexity of devices permit choices among surgical or catheter-based interventional options that optimize short- and long-term patient management. The recognition and understanding of complications of these devices, many of them related to the biomaterials that comprise them, has led to iterative efforts to improve their performance and safety through biomaterials and device research and development. The result has been highly significant improvements, which have been translated into better patient care. The nature, frequency, and pathologic anatomy of their complications, as well as the responsible blood–tissue–biomaterials interaction mechanisms, have been published for widely used devices used for many years, but are less well appreciated for recently introduced or modified devices and those currently in development (Schoen and Gotlieb, 2016; Buja and Schoen, 2016).

This chapter and the one following summarize key considerations in cardiovascular medical devices, including the

underlying pathology of the conditions they are designed for and used to treat, relevant biomaterials information, and the most important complications that need to be circumvented. The first chapter emphasizes biomaterials and engineering design issues relevant to cardiac valve prostheses, which have been used extensively for approximately six decades and are clinically important; the outcomes and pathological descriptions of complications encountered with many different types of valve prostheses are well known. The chapter also discusses pacemakers and implantable cardioverter-defibrillators (ICDs), implantable cardiac assist devices and artificial hearts, and miscellaneous intracardiac devices, including percutaneous catheter-based techniques to treat cardiovascular disease in a minimally invasive manner, such as septal defect closure devices, and left atrial occlusion devices. The second chapter discusses devices used for vascular repair and replacement (including vascular grafts and endovascular stents and stent grafts), filters to prevent pulmonary embolism, and other catheters and cardiovascular devices that reside outside the heart.

## Heart Valve Function and Valvular Heart Disease

The four intracardiac valves play a critical role in assuring unidirectional forward blood flow through the heart. The tricuspid valve allows one-way flow from the right atrium to the right ventricle, and correspondingly the pulmonary valve from the right ventricle to the pulmonary artery, the mitral valve from the left atrium to the left ventricle, and the aortic valve from the left ventricle to the aorta. The heart valves open and close with each cardiac cycle, i.e., approximately once per second, which equates to approximately 40 million times per year and 3 billion times in a 75-year lifetime.

Disorders of heart valves can cause stenosis (i.e., obstruction to flow) or regurgitation (i.e., reverse flow across the valve) (Schoen and Mitchell, 2015; Schoen and Butany, 2016). Sometimes, both stenosis and regurgitation are present in the same valve. Some disease processes such as infective endocarditis (infection of a heart valve) can cause rapid (in days) destruction of the affected valve and lead to abrupt heart failure and death, while others such as calcific aortic stenosis can take many decades to develop clinical manifestations. Progress has been made in recent years toward elucidating a conceptual framework that integrates the dynamic functional structure of heart valves from macro- to micro- to ultrastructure, the biomechanical properties, and the pathobiological behavior of the cardiac valves (Ayoub et al., 2017).

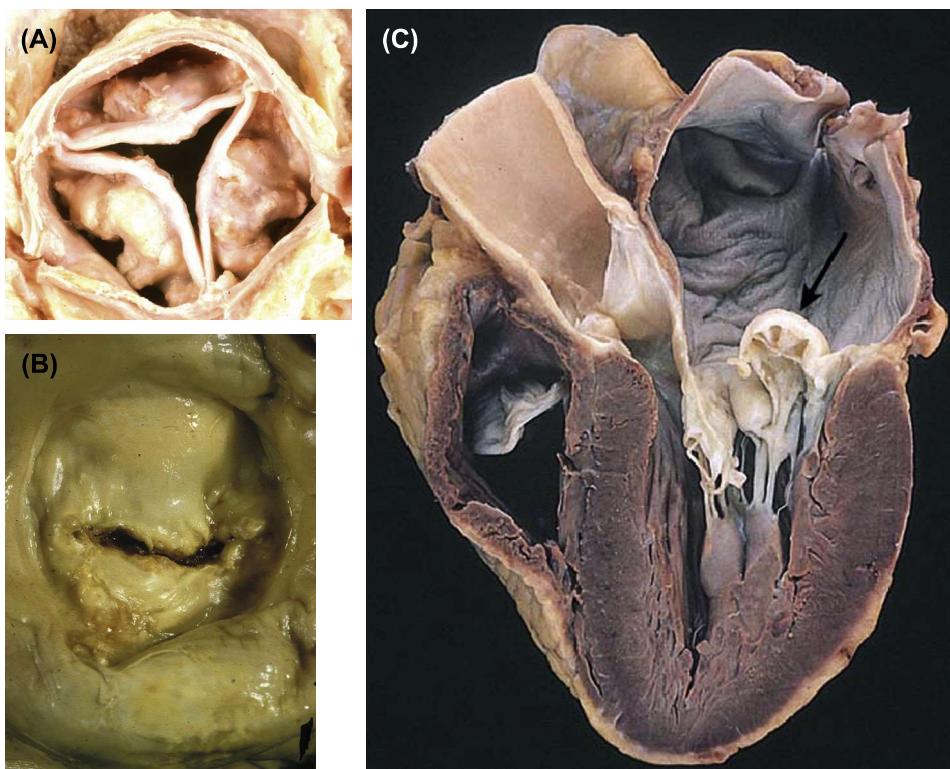
There are several major forms of valvular heart disease; most involve the aortic and/or the mitral valve. The most common type of valve disease and most frequent indication for valve replacement overall is calcific aortic stenosis—obstruction at the aortic valve secondary to age-related calcification of the cusps of a valve that was previously anatomically normal

(Fig. 2.5.2A.1A) (Carabello and Paulus, 2009). Elucidating the precise mechanisms of calcification of the aortic valve has been elusive, but recent insights have been gained through the study of the effects of continuous and cyclical mechanical forces on the behavior of the valvular interstitial cells and the associated inflammatory cytokine milieu within the valve tissue (Merryman and Schoen, 2013). Calcific nodules form in the valve cusps, which do not allow the valve to fully open, resulting in pressure overload of the left ventricle, which induces hypertrophy (enlargement of the mass) of the walls of this chamber. This condition takes decades to develop and typically produces symptoms in approximately the seventh and eighth decades of life.

Although the normal aortic valve has three cusps, 1%–2% of all individuals are born with a bicuspid aortic valve (i.e., with only two cusps), a condition called congenital bicuspid aortic valve (Mathieu et al., 2015). A congenitally bicuspid valve generally functions well initially and into adulthood, but persons who have this condition develop valve dysfunction and thereby symptoms at relatively younger ages—approximately 10 years earlier than in a patient having a valve with three cusps.

Aortic regurgitation (also known as insufficiency) is a less frequent but nevertheless important problem, most often caused by dilation of the aortic root. This prevents complete and effective closure of the cusps, allowing backflow across the valve and leading to volume overload of the left ventricle (Goldberg and Halperin, 2008). Mitral stenosis (Fig. 2.5.2A.1B) has a single predominant cause—chronic rheumatic heart disease—which leads to scarring and stiffening of the mitral leaflets. This condition usually becomes clinically manifest many years or even decades following an episode of acute rheumatic fever secondary to streptococcal pharyngitis (a common form of childhood throat infection) (Chandrashekhar et al., 2009). Mitral regurgitation, on the other hand, results from many different conditions; the most frequent is myxomatous valve degeneration (also known as floppy mitral valve), in which the strength of the mitral valve tissue is deficient, thereby causing the valve leaflets to deform excessively (Carabello, 2008) (Fig. 2.5.2A.1C). Conditions in which the left ventricle is abnormally dilated and/or scarred and consequently the valve is not supported properly, and infective endocarditis (i.e., infection of the valve), are among the other major causes of mitral regurgitation.

Diseases of the right-sided valves (tricuspid and pulmonary) are much less common than those of the left-sided valves. However, in children with congenital heart disease, there is a need for valves in the pulmonary position (in addition to left-sided valves); replacement of valves for congenital anomalies account for approximately 5% of valve replacements (Barnett and Ad, 2009). The major clinical complication of valvular heart disease is cardiac failure secondary to changes in the myocardium induced by pressure or volume overload of the chambers either upstream or downstream of the diseased valve.



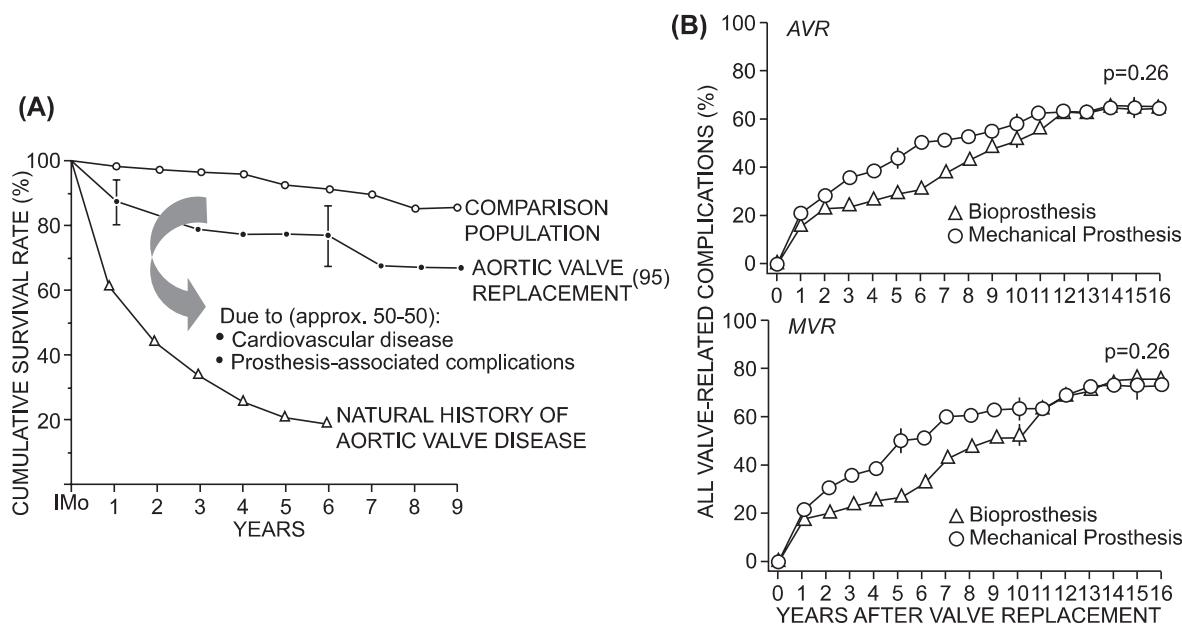
**• Figure 2.5.2A.1** Types of heart valve disease. (A) Severe degenerative calcification of a previously anatomically normal tricuspid aortic valve, the predominant cause of aortic stenosis, and the leading form of valvular heart disease. (B) Chronic rheumatic heart disease, manifest as mitral stenosis, viewed from the left atrium. (C) Myxomatous degeneration of the mitral valve, demonstrating hooding with prolapse of the posterior mitral leaflet into the left atrium (arrow). ((A, B) Reproduced by permission from Schoen, F.J., Edwards, W.D., 2001. Valvular heart disease: General principles and stenosis. In: Silver, M.D., Gotlieb, A.I., Schoen, F.J. (Eds.), *Cardiovascular Pathology*, third ed. Churchill Livingstone, New York. (C) Reproduced by permission from Schoen, F.J., Mitchell, R.N., 2015. The heart. In: Kumar, V., et al., (Eds.), *Robbins Pathologic Basis of Disease*, ninth ed. W.B. Saunders, Philadelphia.)

Heart valve disease is common and serious, and individuals with its various forms have significant mortality and morbidity. For example, the mortality of nonsurgically treated critical aortic stenosis, the most deleterious functional abnormality, is approximately 50% at 2–3 years following the onset of symptoms (Fig. 2.5.2A.2A); thus this natural history is more severe than that of many cancers. Valve replacement is a highly beneficial therapy for such patients; survival following valve replacement is 50%–70% and serious complication-free survival is approximately 30%–50% at 10–15 years (Rahimtoola, 2003). Operative mortality for aortic and mitral valve replacement is 3% and 6%, respectively. While valve replacement thus provides a substantial improvement over the natural history of disease, patients with artificial valves can suffer complications related to the device (Fig. 2.5.2A.2A).

The surgical treatments available for valvular heart disease include replacement of the valve with a prosthesis and repair of the existing abnormal valve tissue to make it functional (Fedak et al., 2008). According to estimates derived from data collected by the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, in 2005, 36,678 individuals had aortic or mitral valve replacement in the United States and 8669 had valve repairs (Barnett and Ad, 2009). Reconstructive/repair procedures to eliminate

mitral insufficiency and to minimize the severity of rheumatic mitral stenosis are now highly effective and commonplace. A recent survey of practice in the United States showed that 69% of mitral valve operations for mitral regurgitation currently use repair rather than replacement (Gammie et al., 2009). Whenever possible, repair of a valve is preferable over replacement; advantages of repair relate to the elimination of both the risk of prosthesis-related complications and the need for chronic anticoagulation that is required in many patients with substitute valves, and mandatory in patients with mechanical valves. Surgical valve repair is often accompanied by stabilization of the annulus with or without implantation of a prosthetic annuloplasty ring. Unfortunately, repair is usually not possible for most forms of aortic valve disease.

When repair is not possible, severe symptomatic valvular heart disease is treated by surgical valve replacement, which comprises excision of part or all of the diseased valve and replacement by a functional substitute. From a design standpoint, the ideal replacement valve would be nonthrombogenic, nonhemolytic, infection resistant, chemically inert, durable, and easily inserted. It would open fully and close quickly and completely, heal appropriately in place, and not be noticed by the patient (for example, it would be noise free) (Harken et al., 1962; Sapirstein and Smith, 2001).



• **Figure 2.5.2A.2** Outcome following cardiac valve replacement. (A) Survival curves for patients with untreated aortic valve stenosis (natural history of valve disease) and aortic valve stenosis corrected by valve replacement, as compared with an age-matched control population without a history of aortic valve stenosis. The numbers presented in this figure for survival following valve replacement nearly four decades ago remain accurate today. This reflects the fact that improvements in valve substitutes and patient management have been balanced by a progressive trend toward operations on older and sicker patients with associated medical illnesses. (B) Frequency of valve-related complications for mechanical and tissue valves following mitral valve replacement (MVR) and aortic valve replacement (AVR). (A) Reproduced by permission from Roberts, L., et al., 1976. Long-term survival following aortic valve replacement. Am. Heart J. 91, 311–317. (B) Reproduced by permission from Hammermeister, K., et al., 2000. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: Final report of the Veterans Affairs Randomized Trial. J. Am. Coll. Cardiol. 36, 1152–1158.)

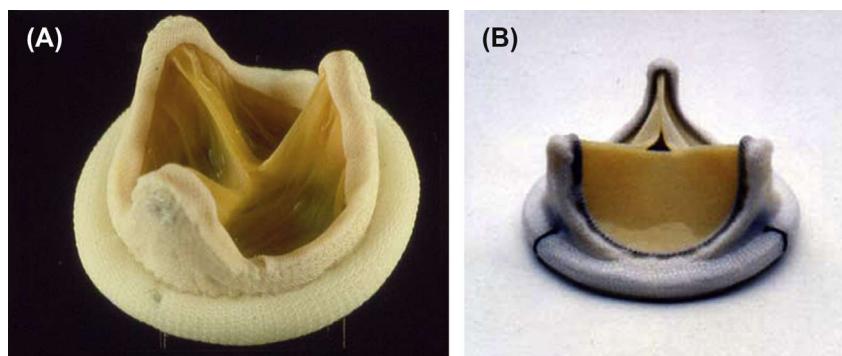
## Surgical Bioprosthetic and Mechanical Heart Valves

The evolution of prosthetic heart valves and related cardiovascular surgical technology was enabled during the first half of the 20th century by multiple key developments, including cardiac catheterization, innovative surgical techniques, cardiopulmonary bypass machines, and the anti-coagulant heparin (Chaikoff, 2007). In the late 1950s, stimulated by collaborations established between surgeons and biomedical engineers, innovative procedures and device technology matured in the surgical research laboratory were translated to clinical practice. These developments fostered new opportunities to replace dysfunctional cardiovascular components with biologic or synthetic prostheses. A key step in modern valve replacement technology was the Hufnagel ball valve, designed to be implanted rapidly into the descending thoracic aorta with the use of proximal and distal fixation rings in patients with aortic regurgitation (Butany et al., 2002). However, with this valve, regurgitant flow from the lower body was prevented, but cardiac work was only partially relieved and coronary flow was not improved. Subsequently, cardiac surgeon Dr. Albert Starr and his colleagues, along with a mechanical engineer, Lowell Edwards, fabricated a valve consisting of a stainless-steel cage, a heat-cured Silastic

ball, and a base surrounded by a Teflon fabric sewing cuff, the latter component permitting the surgeon to suture the valve in place orthotopically (i.e., in the anatomically appropriate location within the heart). The three generic components just described, moving part (either synthetic or biologic), superstructure to guide the motion of the moving occluder, and sewing cuff (anchored at the anastomotic site), comprise the key parts of all previous and present surgical heart valve prostheses. Now used extensively for more than a half century, cardiac valve prostheses are a clinically important achievement of biomaterials science and biomedical engineering. Indeed, the prestigious 2007 Lasker Award for Clinical Medical Research was granted to Drs. Albert Starr and Alain Carpentier to recognize the importance of cardiac valve replacement as a major clinical success (Chaikoff, 2007; Lifton, 2007). Starr performed the first successful valve replacement in the heart in 1960 by implanting a caged-ball mechanical valve prosthesis in the mitral position (Starr, 2007). Carpentier fabricated a “bioprosthetic,” combining chemically treated biologic tissue and a mechanical structure to create a tissue-based (though nonliving) heart valve replacement (Carpentier, 2007). Relevant outcome data and pathological descriptions of complications of many different types of valve prostheses are well known (Vongpatanasin et al., 1996; Bonow et al., 2006; Schoen and Butany, 2016).



• **Figure 2.5.2A.3** Mechanical prosthetic heart valves. (A) Starr-Edwards caged-ball valve. (B) Bjork-Shiley tilting disk valve. (C) St. Jude Medical bileaflet tilting disk heart valve. (Reproduced by permission from Schoen, F.J., 2001. Pathology of heart valve substitution with mechanical and tissue prostheses. In: Silver, M.D., Gotlieb, A.I., Schoen, F.J. (Eds.), *Cardiovascular Pathology*, third ed. Churchill Livingstone, New York.)



• **Figure 2.5.2A.4** Tissue heart valve replacement devices. (A) Hancock porcine valve. (B) Carpentier-Edwards bovine pericardial valve. (Reproduced by permission from Schoen, F.J., 2001. Pathology of heart valve substitution with mechanical and tissue prostheses. In: Silver, M.D., Gotlieb, A.I., Schoen, F.J. (Eds.), *Cardiovascular Pathology*, third ed. Churchill Livingstone, New York.)

The achievements of Starr and Carpentier provided the foundation on which the clinical success of heart valve replacement is built. Today, more than 80,000 valves are replaced each year in the United States and more than 275,000 worldwide. Moreover, devices and techniques for minimally invasive and percutaneous (catheter-based) valve replacement and repair and other interventional techniques are undergoing rapid innovation and development, and there has been exciting progress toward the creation of a living tissue-engineered heart valve replacement.

Hundreds of designs of substitute heart valve replacement devices have been explored experimentally and in patients; most have been abandoned because of design and materials deficiencies that manifest in complications that became apparent only in clinical use (Dewall et al., 2000; Edmunds, 2001; Schoen and Butany, 2016). The opening and closing of a prosthetic valve are purely passive, with the moving parts (occluder or disk[s]) responding to changes in pressure and blood flow within the chambers of the heart and great vessels. Today's cardiac valvular substitutes are of two generic types: mechanical valves and biological tissue valves. The choice of which valve to use in a particular patient is often difficult (Rahimtulla, 2003; Head et al., 2017; Hirji et al., 2018), even though the overall complication rates for mechanical versus bioprosthetic valves is similar over time in both the aortic and mitral positions (Fig. 2.5.2A.2B).

Mechanical prosthetic heart valves (Fig. 2.5.2A.3) are composed of nonphysiologic biomaterials that employ rigid, mobile occluders in a metallic cage (cobalt-chrome or titanium alloy) as in the Bjork-Shiley, Hall-Medtronic, and OmniScience valves, or two carbon hemidisks in a carbon housing as in the St. Jude Medical (the most widely used), CarboMedics CPHV, Medical Carbon Research Institute, or On-X prostheses. Visually, mechanical valves do not resemble the natural heart valves. Today, all mechanical valve occluders are fabricated from pyrolytic carbon. Pyrolytic carbon has high strength, fatigue and wear resistance, and exceptional biocompatibility, including relative thromboresistance. Patients receiving mechanical valves must be treated with lifelong anticoagulation to reduce the risk of thrombosis and thromboembolic events.

Having a trileaflet configuration with a central orifice, tissue valves (Fig. 2.5.2A.4) resemble natural valves. The term "bioprosthetic" describes a special type of tissue valve composed of three cusps of tissue derived from animals—most frequently either a porcine (pig) aortic valve or bovine (cow) pericardium—each treated with glutaraldehyde. Glutaraldehyde fixation preserves the tissue, decreases its (already relatively low) immunological reactivity, and kills the cells within the valve tissue. No immunosuppression is required for these xenografts as is required for whole organ transplants (e.g., kidney, liver, or heart). However, since

these valves no longer contain viable cells, the cusps themselves cannot remodel or respond to injury as does normal tissue. Fabricated tissue valve cusps are usually mounted on a metal or plastic stent with three posts (or struts) to simulate the geometry of a native semilunar valve. As with mechanical valves, the base ring is covered by a Dacron- or Teflon-covered sewing cuff to facilitate surgical implantation and healing. The most widely used valve type is the Carpentier-Edwards pericardial valve.

Also used occasionally are tissue valves derived from human cadaveric aortic or pulmonary valves with or without the associated vascular conduit (called allografts, or homografts). These valves have good hemodynamic profiles, a low incidence of thromboembolic complications without chronic anticoagulation, and a low reinfection rate following valve replacement for endocarditis (O'Brien et al., 2001). Several decades ago, when the use of valve allografts began, they were sterilized and/or preserved with chemicals or irradiation; such valves suffered a high rate of leaflet calcification and rupture. Subsequent technical developments have led to the current practice—allografts that are cryopreserved rather than chemically preserved. Freezing is performed with protection from ice crystal formation using dimethyl-sulfoxide. The valves are subsequently stored until use at  $-196^{\circ}\text{C}$  in liquid nitrogen. Contemporary allograft valves yield freedom from degeneration and tissue failure equal to or better than those of conventional porcine bioprosthetic valves, but their use is limited by availability, difficulty in obtaining the proper size, and a more complex surgical procedure for implantation.

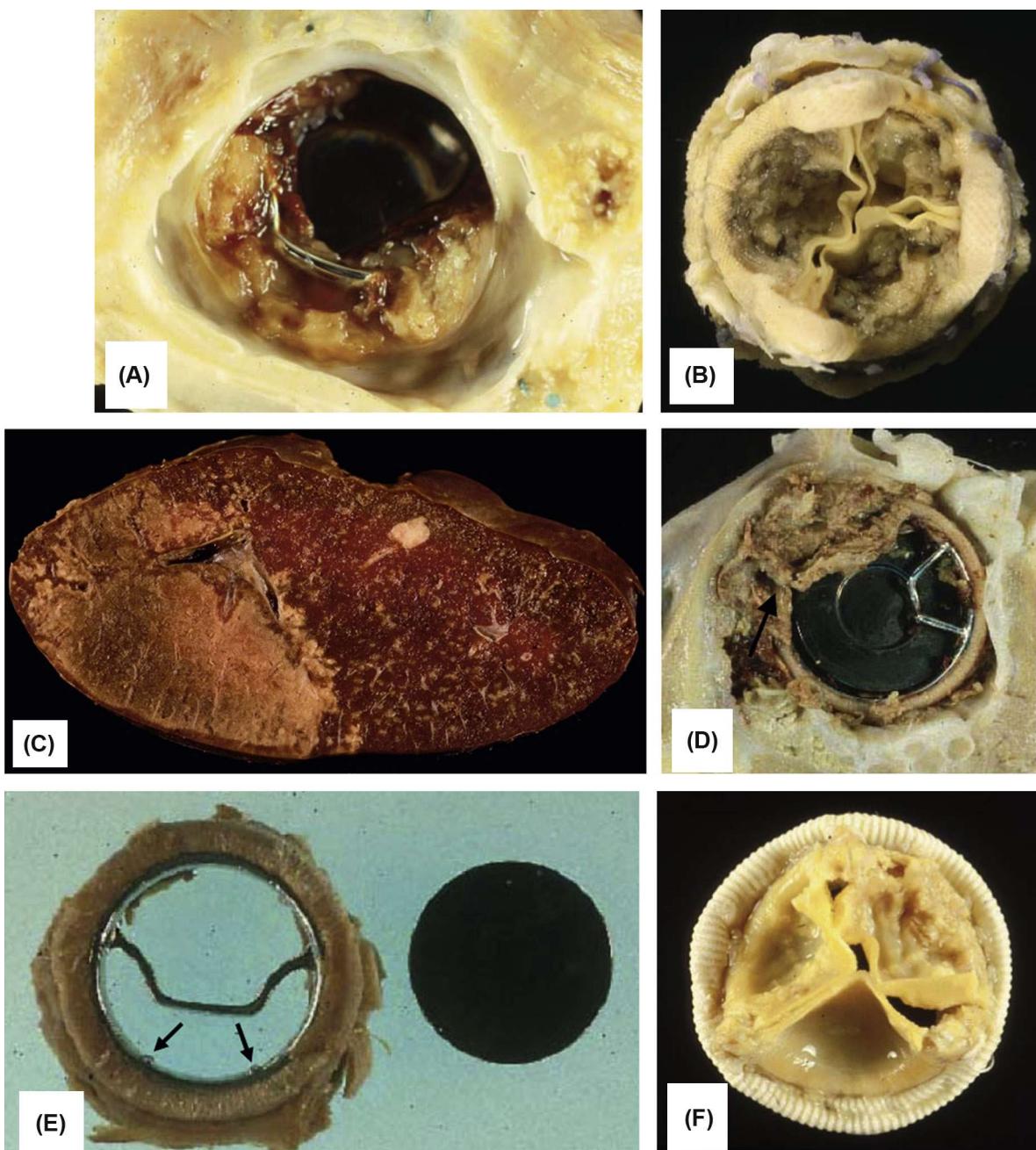
The reliability of a valve prosthesis and its interactions with the host and local tissues play a major role in patient outcome. Four categories of valve-related complications have been most important in limiting success (Fig. 2.5.2A.5): thrombosis and thromboembolism, infection, structural dysfunction (i.e., failure or degeneration of the biomaterials comprising a prosthesis), and nonstructural dysfunction (i.e., miscellaneous complications and modes of failure not encompassed in the previous groups). The major advantages of tissue valves compared to mechanical prostheses are their pseudoanatomic central flow and relative nonthrombogenicity (see later); consequently, patients with tissue valves usually do not require anticoagulant therapy unless they have atrial fibrillation (AF) or another specific propensity to thrombose the valve.

Thromboembolic complications are the major cause of mortality and morbidity after cardiac valve replacement with mechanical valves. No synthetic or modified biological surface is as resistant to thrombosis (*thromboresistant*) as normal unperturbed endothelium. As in the cardiovascular system in general, Virchow's triad (surface thrombogenicity, hypercoagulability, and locally static blood flow) largely predicts the relative propensity of a device to thrombus formation and location of thrombotic deposits with cardiovascular prostheses (Bennett et al., 2009). Exposure of blood to an artificial surface can induce thrombosis, embolization, and consumption of platelets and plasma coagulation factors, as well as

the systemic effects of activated coagulation, complement products, and platelets. Thus patients who have received mechanical substitute heart valves require lifetime therapeutic anticoagulation with warfarin derivatives, which induces a risk of hemorrhage, is potentially serious, and in some cases is fatal (Vahanian, 2008). Thrombotic deposits forming on valve prostheses can immobilize the occluder or shed emboli to downstream arterial beds (Fig. 2.5.2A.5A–C).

Prosthetic valve infection (endocarditis) occurs in 3%–6% of recipients of substitute valves (Fig. 2.5.2A.5D). When endocarditis was the reason for the original valve replacement, the risk is markedly increased. Rates of infection of bioprostheses and mechanical valves are similar. However, since mechanical valve biomaterials cannot themselves become infected, endocarditis on mechanical valves is localized to the prosthesis/tissue junction at the sewing ring, with accompanying tissue destruction in this area (Piper et al., 2001). While bioprosthetic valve endocarditis can also be localized to the host tissue/prosthesis junction, biological tissue (despite being chemically fixed) can support growth of bacteria and other microorganisms, and thus the cusps are involved in some cases. The most frequent portals of entry include the mouth via dental procedures, urologic infections and interventions, and indwelling catheters; all comprise breaches of a natural mucosal or cutaneous barrier that may release organisms into the blood. Prosthetic valve endocarditis can occur either early (less than 60 days postoperatively) or late (can be years). The microbial etiology of early prosthetic valve endocarditis is dominated by the staphylococcal species *Staphylococcus epidermidis* and *Staphylococcus aureus*, even though prophylactic antibiotic regimens used routinely at the time of implantation are targeted against these microorganisms. The clinical course of early prosthetic valve endocarditis tends to be fulminant. The most common organisms in late prosthetic valve endocarditis are *S. epidermidis*, *S. aureus*, *Streptococcus viridans*, and *Enterococci*. Prosthetic valve endocarditis is very difficult to eradicate by antibiotics alone, and thus usually necessitates surgical reintervention.

Prosthetic valve dysfunction because of materials degradation can necessitate reoperation or cause prosthesis-associated death. Many valve models have been withdrawn from clinical use because of poor durability. Durability considerations vary widely for mechanical valves and bioprostheses, for specific types of each, for different models of a particular prosthesis utilizing different materials or having different design features, and even for the same model prosthesis placed in the aortic rather than the mitral position. Fractures of metallic or carbon components of mechanical valve prostheses are usually catastrophic but are fortunately rare (Fig. 2.5.2A.5E). Contemporary single-leaflet or bileaflet tilting disk valves with pyrolytic carbon occluders and either metallic struts or carbon housing have generally favorable durability. Fractures related to past design defects are noteworthy in two valve cohorts. In one instance, the Bjork-Shiley single-leaflet tilting disk valve was redesigned with the intention of enhancing disk opening and



**• Figure 2.5A.5** Complications of prosthetic heart valves. (A) Thrombosis on a Bjork-Shiley tilting disk aortic valve prosthesis, localized to outflow strut near minor orifice, a point of flow stasis. (B) Thrombosis of Hancock porcine bioprosthetic valve. (C) Thromboembolic infarct of the spleen (light area on left) secondary to embolus from valve prosthesis. (D) Prosthetic valve endocarditis with large ring abscess (arrow), viewed from the ventricular aspect of an aortic Bjork-Shiley tilting disk aortic valve. (E) Strut fracture of Bjork-Shiley valve, showing valve housing with single remaining strut and adjacent disk. Sites of prior attachment of missing fractured strut designated by arrows. (F) Structural valve dysfunction (manifest as calcific degeneration with cuspal tear) of porcine valve. ((D) Reproduced by permission from Schoen, F.J., 1987. Cardiac valve prostheses: pathological and bioengineering considerations. *J. Card. Surg.* 2 (65). (A and E) Reproduced by permission from Schoen, F.J., Levy, R.J., Piehler, H.R., 1992. Pathological considerations in replacement cardiac valves. *Cardiovasc. Pathol.* 1 (29).)

relieving obstruction and thromboembolic complications that occurred with the original and widely used model. The resultant Bjork-Shiley 60- and 70-degree convexo-concave tilting disk valves suffered fractures of the welded metallic outlet strut and separation from the valve, leading

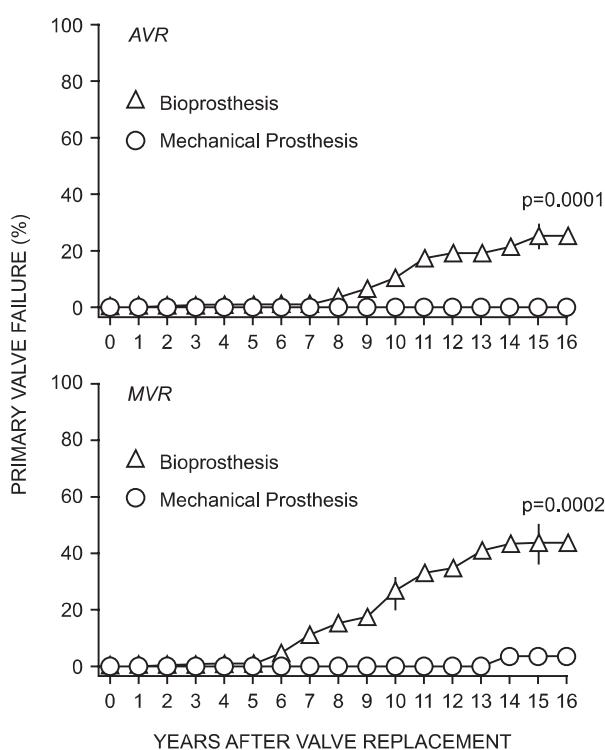
to frequently fatal disk escape (Blot et al., 2005; Harrison et al., 2013). Over 80,000 valves of this model were implanted and at least 600 fractured in this manner. The underlying problem was due to the unanticipated consequence of disk closure at a higher velocity and force, causing

the overrotation and an excessively hard contact with the metallic outlet strut. When the outlet strut stress exceeded its endurance limit, fatigue fracture occurred, most frequently in the region of the welds anchoring this strut to the housing. In another instance, fractures of carbon valve components (hemicdisk or housing) occurred in implanted Edwards (previously Hemex)-Duromedics bileaflet tilting disk valves. At least 46 valves of this type failed in this manner (Mastroroberto et al., 2000). Studies of these explants suggest that valve fracture with leaflet escape resulted from variable combinations of five factors: (1) microporosity in the pyrolytic carbon coating in the leaflets, (2) cavitation bubbles impacting on the carbon surfaces during function, (3) unusual combinations of dimensional tolerances, (4) poor shock-absorbing qualities of the annular tissues in some patients (perhaps due to calcification-induced rigidity), and (5) structural defects in the valve prosthesis induced by fabrication or surgical mishandling. Fractures of carbon components have been encountered only rarely with other carbon bileaflet tilting disk valves, such as the St. Jude Medical valve.

In contrast, structural valve failure with dysfunction is frequent and is the major cause of failure of the most widely used bioprostheses (Fig. 2.5.2A.5F). Bioprosthetic valve structural tissue failure usually results in progressive symptomatic deterioration, which requires reoperation (Schoen and Levy, 2005). Within 15 years following implantation, 30%–50% of porcine aortic valves implanted as either mitral or aortic valve replacements require replacement because of primary tissue failure (Fig. 2.5.2A.6). Cuspal calcification (see Chapter 2.4.5) is the major responsible pathologic mechanism, with regurgitation through tears the most frequent failure mode in porcine valves. The more frequently used contemporary bovine pericardial valves also suffer design-related tearing and/or calcification. Calcification is markedly accelerated in younger patients, with children and adolescents having an especially accelerated course (Saleeb et al., 2014).

Within the group of complications causing nonstructural failure are those that relate to healing of the valve in the site of implantation, either too little or too much. Inadequate healing can cause paravalvular leaks, which permit reverse flow usually through a relatively small defect at the junction of prosthesis and host tissue when the valve is closed. Paravalvular leaks may be clinically inconsequential, may cause hemolysis (i.e., destruction of red blood cells through mechanical destruction of their membranes by the high shear stresses engendered by blood being forced at high velocity through small spaces), or may cause heart failure through regurgitation. In contrast, overexuberant healing, called tissue overgrowth (or pannus), can block occluder motion or lead to secondary thrombus.

Various incremental improvements to valve prostheses are being investigated in preclinical studies and clinical research and implementation. For example, methods are being actively studied and some are being used clinically to prevent calcification of bioprosthetic valves. The confidence engendered by early data that these methods may have extended the durable



• **Figure 2.5.2A.6** Frequency of primary valve failure (nonthrombotic valve obstruction or central valvular regurgitation) for mechanical and tissue valves following mitral valve replacement (MVR) and aortic valve replacement (AVR). Cuspal mineralization is the major responsible pathologic mechanism with regurgitation through tears the most frequent failure mode. (Reproduced by permission from Hammermeister, K., et al., 2000. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: Final report of the Veterans Affairs Randomized Trial. *J. Am. Coll. Cardiol.* 36, 1152–1158.)

lifetime of bioprosthetic valves has led to a dramatic resurgence of their use. Thus as reflected in overall heart valve replacement industry data, innovations in tissue valve technologies and design have stimulated this segment of the market to grow disproportionately in the last decade by expanding indications for tissue valve use and potentially enhanced durability. Thus there has been a trend toward an increasing fraction of tissue valves implanted relative to mechanical valves. Tissue valve use continues to expand, and studies estimate that tissue valves now represent as much as 80% of all substitute heart valves used in some countries (Mohr, 2014; Isaacs et al., 2015; Goldstone et al., 2017). The trend toward increasing use of bioprostheses (relative to mechanical valves) is especially high in older recipients, who generally have diminished rates of calcific failure and in whom anticoagulation carries increased risk of serious hemorrhage.

The advent of so-called sutureless valves for aortic valve disease has allowed for quicker implantations using a more minimally invasive surgical approach (Zannis et al., 2012). The surgery involves removing the diseased aortic cusps and deploying the sutureless valve device. While the valves are implanted surgically, they incorporate several design features discussed later for percutaneous transcatheter valves. The 3f Enable valve (Medtronic, Inc., Minneapolis, MN) consists of three equal pieces of equine pericardium mounted

on a self-expanding Nitinol frame, which contains a polyester flange on the inflow aspect to prevent migration and minimize paravalvular leak. The Perceval S valve (LivaNova, London, UK) contains bovine pericardial cusps mounted within a Nitinol frame. The frame consists of proximal and distal segments with connecting elements to support the valve cusps and allow anchoring to the aortic root. Both of these valves have shown promise clinically for selected patient populations (Chauvette et al., 2018; Fuzellier et al., 2016).

Other approaches to provide improved valves include modifications of bioprosthetic valve stent design and tissue-mounting techniques to reduce cuspal stresses, tissue treatment modifying or an alternative to conventional glutaraldehyde pretreatment to enhance durability and post-implantation biocompatibility, and minimally cross-linked autologous pericardial valves. Near-anatomic configuration, central flow trileaflet prostheses using three flexible synthetic polymeric leaflets in an anatomy that resemble the natural aortic valve, may be facilitated by major developments in the technology of polymeric materials, particularly in the thermoplastic polyurethanes (Bezuidenhout et al., 2015). Although a polymer valve has been used clinically in a cardiac assist device (Leat and Fisher, 1993), durability limitations have been the major concern in an orthotopic (in the natural site) flexible polymeric valve replacement, with preclinical valve failures being marked by thrombosis, tearing, and/or calcification of the cusps (Fishbein et al., 1975; Claiborne et al., 2012). Sutureless valves provide the opportunity in minimally invasive and conventional aortic valve surgery to minimize aortic cross-clamp time and maximize effective valve area. Performance and safety have been demonstrated for up to 5 years (Meuris et al., 2015; Di Eusanio and Phan, 2015).

Scientific and technological progress has stimulated the goal of generating a living valve replacement that would obviate the complications of conventional valve replacement, adapt to changing environmental conditions in the recipient, and potentially grow with a growing patient (Schoen, 2011; Rippel et al., 2012; Bouting et al., 2012; Emmert et al., 2014). The long-term success of a tissue-engineered (living) valve replacement will depend on the ability of its viable cellular components (particularly valvular interstitial cells) to assume normal function with the capacity to repair structural injury, remodel the extracellular matrix, and potentially grow in a growing patient. Translational challenges are substantial (Rabkin et al., 2002; Stassen et al., 2017; Zhang et al. 2019).

Tissue-engineered heart valves grown as valved conduits from autologous cells (either vascular wall cells or bone marrow-derived mesenchymal stem cells) seeded on biodegradable synthetic polymers (e.g., polyglycolic acid mesh coated in poly-4-hydroxybutyrate) grown in vitro have functioned in the pulmonary circulation of growing lambs for up to 5 months (Hoerstrup et al., 2000; Rabkin et al., 2002). In some studies, these grafts evolved in vivo to a specialized layered structure that resembled that of a native semilunar valve. Pulmonary vascular walls fabricated from vascular

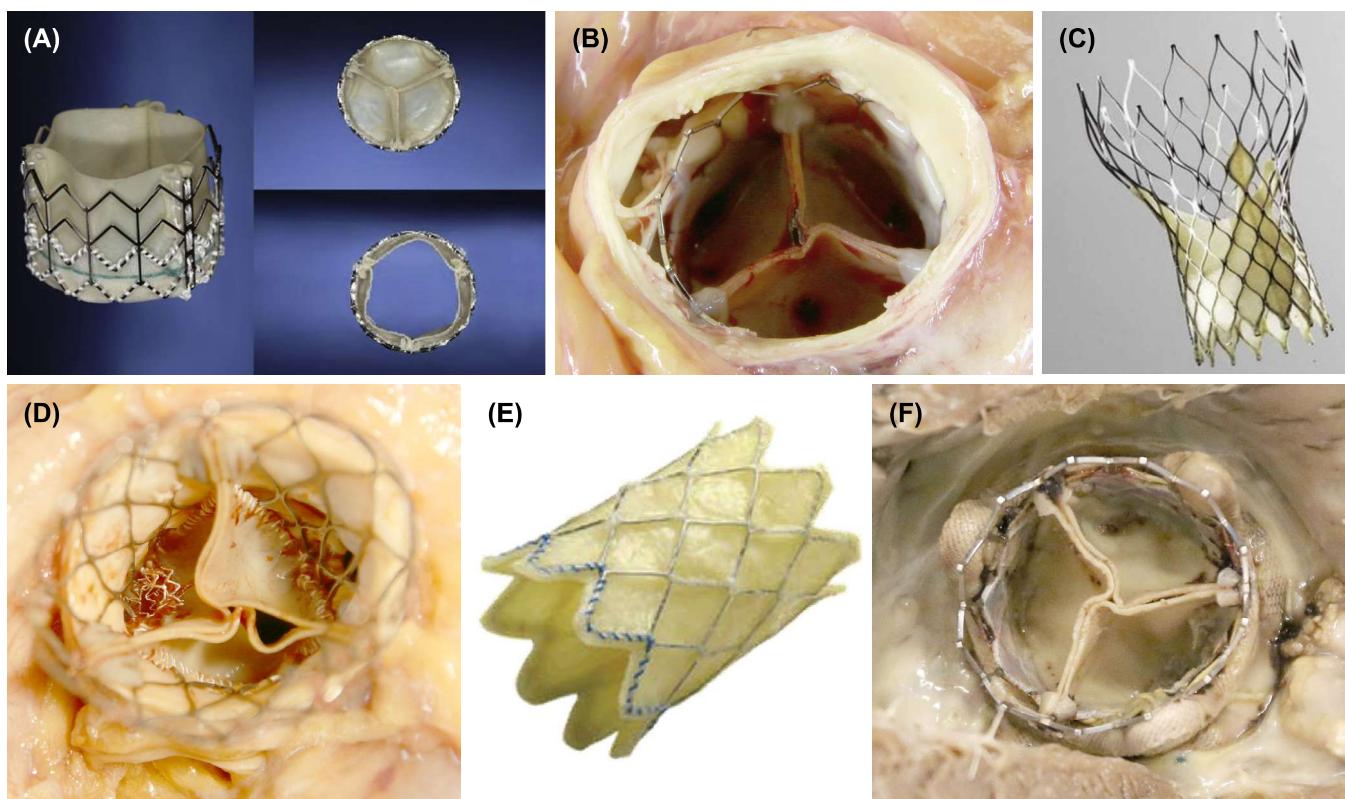
wall cells and biodegradable polymer and implanted into very young lambs enlarged proportionally to overall animal growth over a 2-year period (Hoerstrup et al., 2006). Innovative heart valve tissue approaches may be enabled by emerging biomaterials technologies, including 3D bio-printing, multilayer biomaterials, metal mesh scaffolds, and decellularized valves (Cheung et al., 2015; Lueders et al., 2014; Zhang et al., 2015; Alavi and Kheradvar, 2015; Masoumi et al., 2014).

To eliminate the need for in vitro cell seeding and culture steps, an alternative tissue-engineering strategy has used a scaffold of either decellularized naturally derived biomaterial (such as animal xenograft or human allograft valve, decellularized sheep intestinal submucosa) or a porous polymer matrix implanted without prior seeding but with the intent of harnessing intrinsic circulating cells to populate and potentially remodel the scaffold (Matheny et al., 2000; Ghazanfari et al., 2015; Boroumand et al., 2018). Tissue-derived scaffolds must possess desirable three-dimensional architecture, mechanical properties, and potential adhesion/migration sites for cell attachment and ingrowth. Nevertheless, decellularized porcine valves implanted in humans had a strong inflammatory response and suffered structural failure (Simon et al., 2003). Work is also being done on cell-seeded, engineered tissue valves for transcatheter implantation (Driessen-Mol et al., 2014).

## Percutaneous Transcatheter Valves and Other Devices

Surgical implantation of bioprosthetic and mechanical valves (discussed previously) has a long and proven track record of success, with symptom and quality of life improvements, and enhanced survival. However, a substantial fraction of patients with aortic stenosis, estimated to be 30%–40% overall, is deemed unsuitable for surgical aortic valve replacement because of advanced age, frailty, and often multiple comorbidities (Goldberg et al., 2007). However, a highly significant development over the past several decades is a minimally invasive alternative to conventional aortic valve replacement, called *transcatheter aortic valve implantation* (TAVI), which was initially used clinically in 2002, and has extended the opportunity for effective mechanical correction of valve disease to a potentially large population of otherwise untreatable individuals (Rodes-Cabau, 2012; Genereux et al., 2012; Hamm et al., 2016). Thus TAVI, with its associated novel valve replacement devices, has rapidly become the new standard of care for many (especially elderly) patients who would otherwise be deemed inoperable.

In contrast to classical open surgical treatment of heart valve disease, catheter-based valve implantation uses peripheral arterial access into the femoral artery via a catheter passed retrograde up the aorta to the aortic valve where a novel type of valve device is deployed (i.e., expanded); thus this procedure avoids opening the chest. Alternatively, the device can be deployed in the heart via an antegrade and minimally invasive surgical approach that exposes the apex



**• Figure 2.5.2A.7** Percutaneous valve replacement technology. (A) The Edwards-Sapien balloon-expandable aortic valve replacement designed for percutaneous implantation, constructed from bovine pericardium attached to a stainless-steel stent. A fabric sealing cuff covers the ventricular aspect to prevent leaks between the prosthesis and surrounding tissues. The valve is mechanically crimped onto a valvuloplasty balloon catheter and expanded within the aortic annulus to displace and exclude the stenotic native valve from the circulation. (B) The Sapien valve in situ, which has been deployed within the aortic valve to treat aortic stenosis, viewed from the ascending aorta. (C) Corevalve aortic bioprosthetic, constructed of bovine pericardium attached to a self-expanding nickel-titanium alloy (Nitinol) stent. The ventricular portion has a high radial force to compress the native valve. The midportion is tapered to avoid interference with the coronary arteries. The aortic portion is flared to provide additional fixation against the wall of the ascending aorta. Nitinol can be made soft at cold temperatures allowing the stent to be tightly compressed within a delivery sheath. Once positioned within the native valve the sheath is withdrawn allowing the stent to assume its predetermined shape. There is adequate radial force to compress the native valve. (D) The Corevalve in situ, which has been deployed within the aortic valve to treat aortic stenosis viewed from the ascending aorta. A coronary artery stent that was placed in the left main coronary artery can be seen peeking through the Nitinol stent of the Corevalve at the left of the image. (E) The Melody pulmonary valve is constructed from a bovine jugular venous valve attached with sutures to a platinum-iridium alloy stent. The relatively delicate venous valve functions well in the pulmonary circulation but is too fragile for use in the systemic circulation. Although often referred to as a pulmonary valve, its maximum expanded diameter of 22 mm largely limits its use for surgically constructed right ventricular to pulmonary artery conduits in the pediatric population. (F) A Sapien valve has been deployed within a failing surgically placed bioprosthetic in the mitral position in a “valve-in-valve” application, viewed from the left ventricle. ((A) and (C) reproduced by permission from Schoen, F.J., Webb, J.G., 2008. Prosthetics and the Heart. In: McManus, B.M., Braunwald, E. (Eds.), *Atlas of Cardiovascular Pathology for the Clinician*, Current Medicine, Philadelphia, 241–256.)

of the left ventricle (called *transapical implantation*). This approach is favored in patients in whom manipulation of catheters through severely atherosclerotic sites in the femoral artery and aorta might dislodge debris leading to emboli. The delivery strategy involves collapsing the device and placing it within a catheter-based sheath; for balloon expandable devices, they must be collapsed over a balloon. In the case of aortic stenosis, the valve device is deployed between the cusps of the calcified aortic valve, pushing the diseased cusps out of the flow stream (i.e., in contrast to

open surgery, the diseased valve tissue is not removed during TAVI—[Fig. 2.5.2A.7B](#)). During TAVI, delivery, positioning, and permanent fixation in the optimal location are critical to procedural success and usually guided by a combination of external imaging modalities.

Clinical experience with TAVI is growing rapidly; since the first clinical implantations in 2002, an estimated 300,000+ TAVI procedures have been performed worldwide. Randomized and observational clinical trials from different countries, including observational studies and

randomized trials, have compared TAVI to classical aortic valve replacement (Smith et al., 2011; Kodali et al., 2012; Kim et al., 2014). The consensus of these studies is that TAVI is at least as good as classical aortic valve replacement in terms of procedure “success” regarding morbidity and mortality in high-risk patients to at least 2 years (Tice et al., 2014; Reardon et al., 2015). TAVI and surgical valve replacement are comparable hemodynamically. Recent data suggest that TAVI may also be an excellent alternative to open surgery in patients with intermediate or lower surgical risk (Reardon et al., 2017; Mack et al., 2019; Popma et al., 2019).

The devices used in transcatheter valve implantation have an outer stent-like structure that contains leaflets. The stent holds open a valve annulus and resists the tendency of a valve annulus or diseased native leaflets to recoil following balloon dilation, supports the valve leaflets, and provides the means for seating the prosthesis in the annulus. Tissues used for the valve component include bovine, equine, or porcine pericardium and bovine jugular venous valves. The stents are made from self-expandable stainless steel, platinum-iridium, or other alloys, or shape-memory materials such as nickel-titanium alloys (e.g., Nitinol).

Several catheter-based devices are currently in various stages of development and clinical use in the aortic and pulmonary position. The two transcatheter aortic valves with the largest clinical experience are the Edwards-Sapien family of devices (Edwards LifeSciences) and the CoreValve ReValving system (Medtronic). The Sapien device is composed of a balloon-expandable stainless-steel stent that houses a bovine pericardial trileaflet valve (Fig. 2.5.2A.7A and B). There is a polymer skirt circumferentially attached to the stent to reduce paravalvular leaks. The CoreValve device is composed of a self-expandable Nitinol stent that houses a porcine pericardial trileaflet valve (Fig. 2.5.2A.7C and D). For children with failed right-ventricular to pulmonary artery devices used to correct certain types of congenital heart defects, the Medtronic Melody transcatheter pulmonary valve, composed of a balloon-expandable platinum-iridium alloy stent that houses a segment of bovine jugular vein with its native venous valve, is threaded from the femoral vein to the inferior vena cava through the right side of the heart (Fig. 2.5.2A.7E) (Lurz et al., 2009). Catheter-based valves may also play a role in the treatment of surgically implanted bioprosthetic valves that are failing due to stenosis or regurgitation in a so-called “valve-in-valve” application in which a new prosthesis is inserted directly into a prior one (Fig. 2.5.2A.7F).

Transcatheter valve implantation presents novel challenges (Fishbein et al., 2014). Valved stents are significantly larger than most existing percutaneous cardiac catheters and devices, and thus vascular access is difficult, potential damage along the course of the catheter passage is possible, and dislodging debris that can become emboli is a significant risk. In the aortic position, there is the potential to impede coronary flow, or interfere with anterior mitral leaflet mobility, the conduction system, or the native diseased

leaflets. Stent architecture may also preclude future catheter access to the coronaries for possible interventions. Secure seating within the aortic annulus or a pulmonary conduit and long-term durability of both the stent and the valve tissue are also major challenges. Surgical complications include most frequently paravalvular leak, vascular injury with hemorrhage, and embolic stroke (Fassa et al., 2013; Van Mieghem et al., 2015). Transcatheter heart valves are also likely susceptible to prosthesis-associated failure modes typical of surgical bioprostheses and unique to their specific design; prosthetic valve endocarditis (Mylotte et al., 2015; Neraqi-Miandoab et al., 2015; Amat-Santos et al., 2015) and structural valve failure due to leaflet calcification and thrombosis are the most frequent complications. A critical unknown in the expanding use of transcatheter techniques is the durability of the prostheses.

Many patients with mitral valve disease also are in need of less invasive transcatheter therapies. The first transcatheter mitral valve replacement (TMVR) in a native valve was performed in 2012. However, the complexities and variability of the mitral valve anatomy and its relationship to neighboring structures have resulted in slower progress with this new therapy compared to the rapid uptake that has occurred with transcatheter aortic valve implantation (Patel and Bapat, 2017; Wyler von Ballmoos et al., 2018). TMVR can be applied to degenerated prosthetic valves and annuloplasty rings or to a wide variety of native mitral valve diseases. In cases of degenerated bioprosthetic valves, annuloplasty ring, and native valve mitral annular calcification, transcatheter heart valves designed for the aortic position can be implanted with high procedural safety and success rates. In the case of native valve mitral regurgitation, the complexities have led to the development of several TMVR systems for native valve disease with different anchoring mechanisms and geometry; all are currently investigational and none are Food and Drug Administration (FDA) approved at this time. Percutaneous mitral valve replacement has been investigated using a device similar to that used for TAVI (Webb et al., 2019).

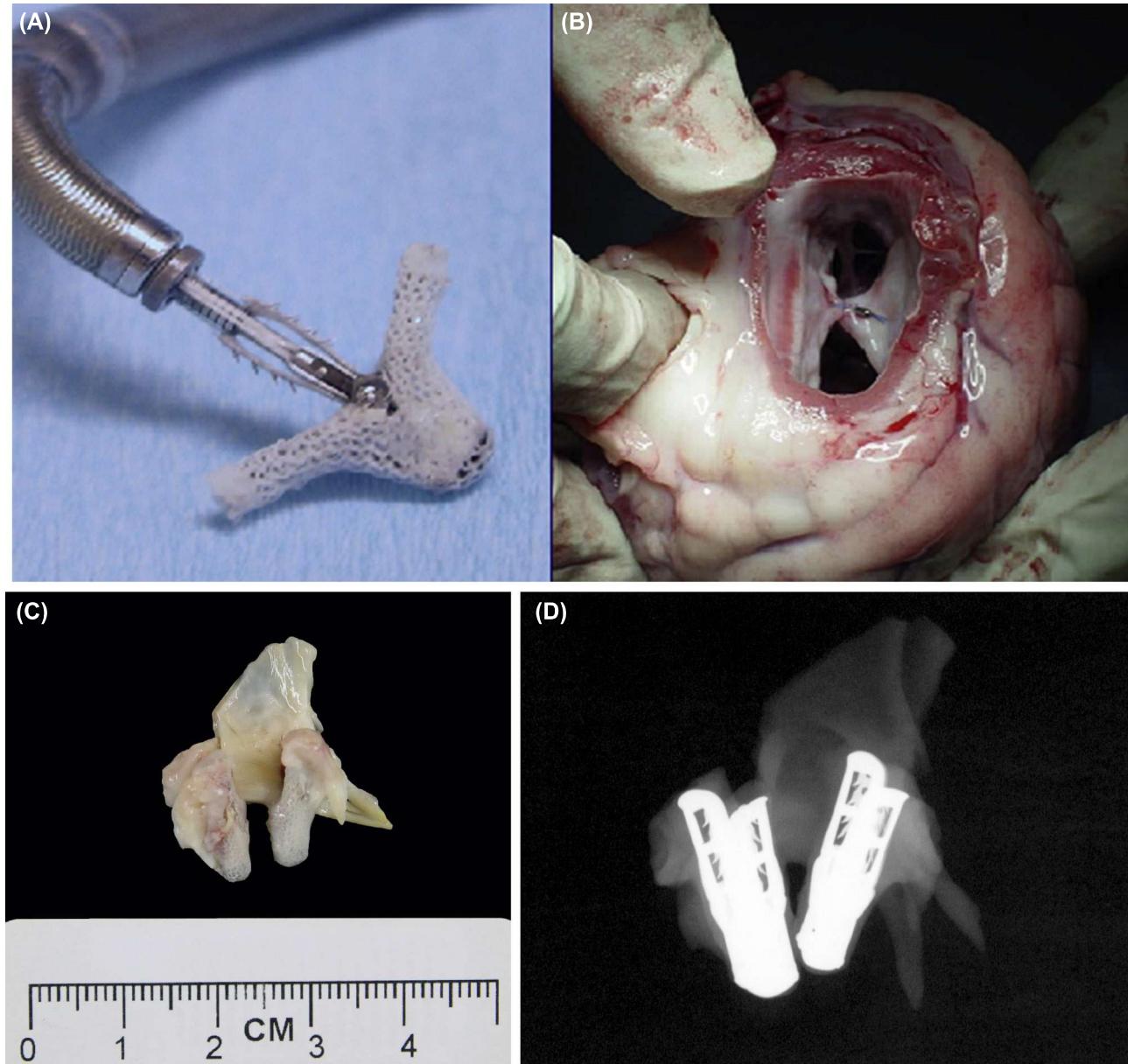
Other percutaneous devices for the treatment of mitral regurgitation are under development or in clinical use. The MitraClip device (Abbott Laboratories, Abbott Park, IL) is a transcatheter-delivered device that reduces mitral regurgitation by fastening the anterior and posterior leaflets together in an edge-to-edge fashion (Panach and Eleid, 2018). Approved in 2013 by the FDA, the device is composed of a polyester-covered implant that consists of two cobalt-chromium metallic arms that can be opened and closed to capture the edges of the anterior and posterior leaflets of the mitral valve (Fig. 2.5.2A.8). When the arms are closed, the leaflets are held together and the valve orifice approximates a “Fig. 2.5.2A.8” with two openings, rather than the single opening of the native valve. The polyester is macroporous, allowing for tissue ingrowth with the goal both of anchoring the device and preventing thrombosis on the foreign material. Clinical studies have been done; a recent clinical trial

of MitraClip versus medical therapy demonstrated safety and efficacy of the device in patients with heart failure due to moderate-to-severe or severe mitral regurgitation (Stone et al., 2018).

## Cardiac Arrhythmias

The normal cardiac electrical cycle (Fig. 2.5.2A.9A) begins with an impulse initiated by the sinoatrial (SA) node, the

heart's natural pacemaker, which is located in the right atrium near the junction with the superior vena cava. The impulse spreads through the muscle of both left and right atrial walls, causing depolarization of the cardiac myocytes that results in atrial contraction. The impulse arrives at the atrioventricular (AV) node, which is located in the posterior right atrium enclosed by the ostium of the coronary sinus, the septal leaflet of the tricuspid valve, and the membranous portion of the interatrial septum (called the

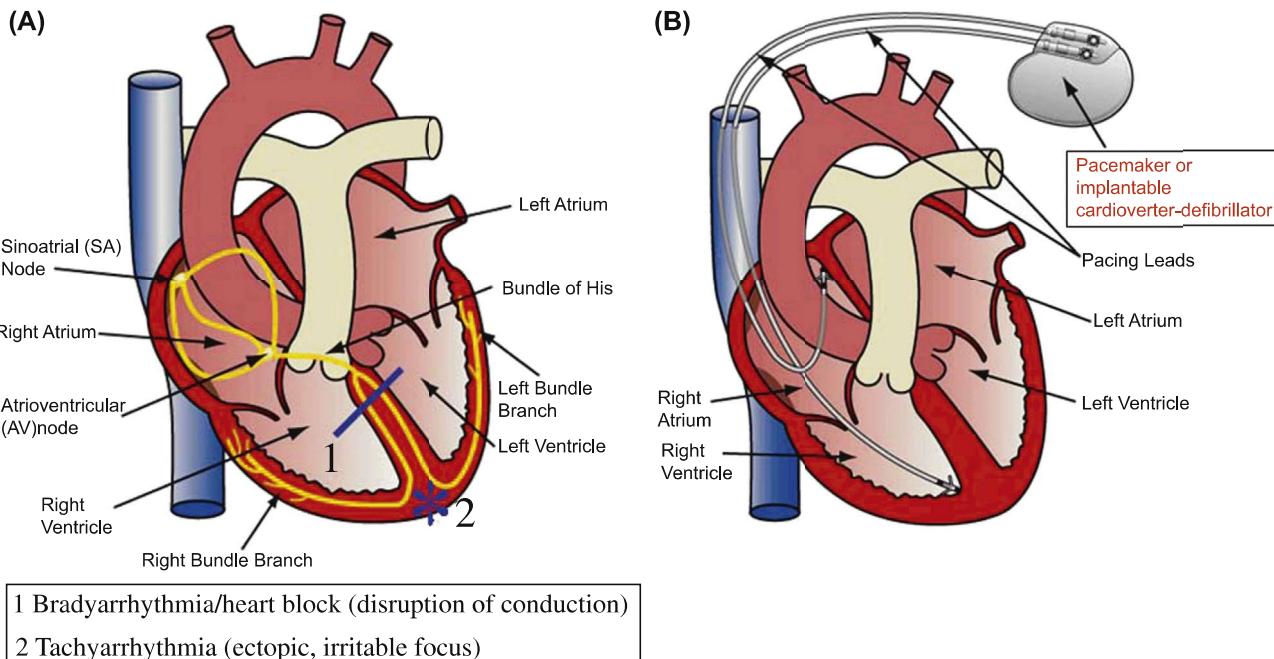


**• Figure 2.5.2A.8** The MitraClip device for mitral regurgitation. (A) MitraClip device on delivery apparatus. (B) Edge-to-edge approximation of the anterior and posterior leaflets of the mitral valve is achieved by deployment of the MitraClip device that is analogous to an Alfieri stitch, thereby creating a double orifice with improved leaflet coaptation. (C) Two MitraClip devices are seen attached to a portion of the mitral valve. The portion of valve and devices were removed surgically during a valve replacement necessitated by worsening mitral regurgitation. The cloth covering has facilitated tissue ingrowth into the device to help passivate the blood-contacting surface and minimize thrombosis. (D) A specimen radiograph shows the structure of the two cobalt-chromium metallic arms in the closed position. ((A) and (B) reproduced with permission from Schoen, F.J., Butany, J., 2016. Cardiac valve replacement and related interventions. In: Buja, L.M., Butany, J. (Eds.), *Cardiovascular Pathology*, fourth ed. Elsevier, 529–576.)

triangle of Koch). After a short delay within the AV node, the impulse passes to the bundle of His and into the left and right bundle branches, located in the intraventricular septum. The impulse spreads through the right and left ventricular myocardium causing a wave of myocyte depolarization and thereby coordinated ventricular contraction. The SA and AV nodes and the bundles of His and its right and

left bundle branches are composed of cardiac muscle cells specialized for conduction.

Cardiac arrhythmias (Huikuri et al., 2001) reflect disturbances of either impulse initiation or impulse conduction. Foci of impulse-generating (automatic) cells outside the SA node, called ectopic foci, may initiate cardiac impulses that generate suboptimal ventricular



• **Figure 2.5.2A.9** Cardiac arrhythmias and device therapy. (A) The normal cardiac electrical cycle showing schematically sites of both conduction blocks and ectopic foci of impulse generation. (B) Schematic demonstrating implantable cardioverter-defibrillator (ICD) lead placement in the right ventricle. (C) Guidant Prizm II DR ICD, introduced to the US market in 2000, and withdrawn in 2005. (D) Transvenous pacing lead placed in right ventricle demonstrating fibrosis of the distal portion of the lead (arrow). (E) Fibrous capsule surrounding pacemaker electrode in the right ventricle. Low-power photomicrograph demonstrating the space previously occupied by the electrode (e), fibrous tissue separating electrode from blood in the right ventricular chamber (between arrows) and extending around the electrode to separate it from myocardium (m), potentially creating a barrier to conduction of the pacing impulse. (F) Micra Transcatheter Pacing System capsule, which is meant to be implanted in the right ventricle as a leadless pacemaker. (G) Photograph depicting failure of the polymer insulation surrounding the wires (blue) of an ICD, allowing the wires to directly contact the myocardium in areas away from the lead tip. ((E) Reproduced by permission from Schoen, F.J., Webb, J.G., 2008. Prosthetics and the Heart. In: McManus, B.M., Braunwald, E. (Eds.), *Atlas of Cardiovascular Pathology for the Clinician*, Current Medicine, Philadelphia, 241–256.)

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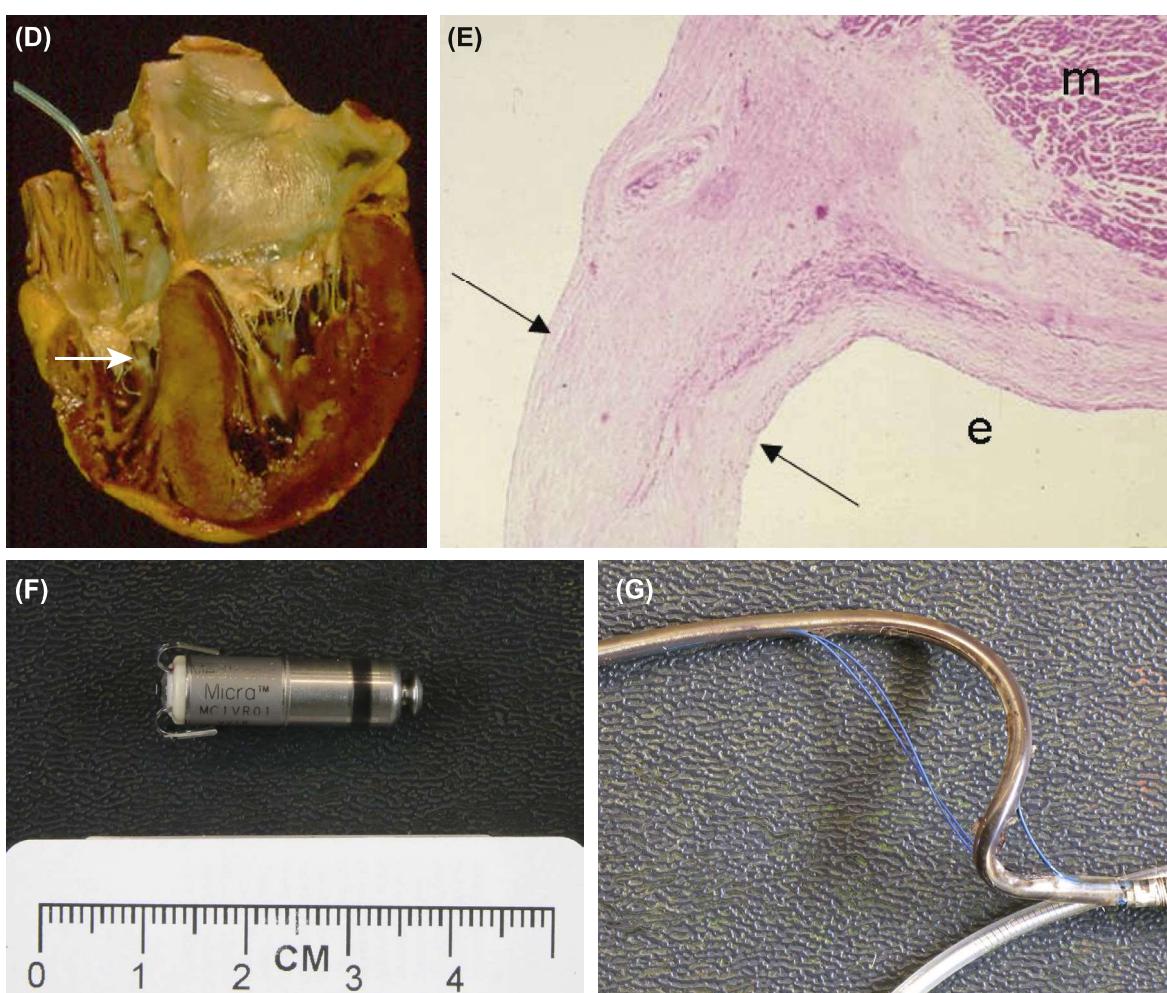


Figure 2.5.2A.9 cont'd

contractions. These arrhythmias are usually fast, i.e., tachyarrhythmias, and can result in ventricular fibrillation, which can be fatal. Intrinsic SA node dysfunction also can account for disturbances of impulse initiation. In contrast, disturbances of impulse conduction mainly consist of conduction blocks or reentry. Conduction blocks constitute a failure of propagation of the usual impulse through the specialized muscle as a result of a disease process (such as ischemia or inflammation) or certain drugs. Blocks can be complete (no impulse propagation) or incomplete (impulse propagates more slowly than normal), and can be permanent or transient. Reentry is said to occur when a cardiac impulse traverses a loop of cardiac fibers and reexcites previously excited tissue without a second impulse from the SA node. For patients in whom these cardiac arrhythmias cannot be controlled pharmacologically by antiarrhythmic drugs, two therapeutic options are available: (1) electrical therapy to control the cardiac rhythm, such as direct current cardioversion or implantable devices such as pacemakers and ICDs, and (2) interventional/surgical therapy to remove the affected tissue or interrupt the abnormal pathway such as endocardial resection, cryoablation, or radiofrequency ablation (Halbfass et al., 2018).

### Cardiac Pacemakers

Cardiac pacemakers are medical devices that provide impulses to the conduction system to initiate contraction. The first cardiac pacemaker was implanted (Atlee and Bernstein, 2001) in 1958 and since then cardiac pacing has become a well-established therapeutic tool. The first pacemakers were large ( $40\text{--}200\text{ cm}^3$ ) by today's standards ( $9\text{--}45\text{ cm}^3$ ) and contained few of the features that are standard in current devices. Over a million patients in the United States currently have pacemakers (Fig. 2.5.2A.9B and C) and over 250,000 new permanent pacemakers are implanted each year; pacemaker placement, revision or removal is a commonly performed procedure. Most cardiac pacemakers are implanted in patients over 60 years old but they are also used in children, including infants, when necessary. The most common indications for permanent cardiac pacing are various types of conduction block. Some conduction blocks lead to bradycardia (abnormally low heart rate), while others, predominantly in the left or right bundles, will result in ventricular dyssynchrony and inefficient ventricular contraction in the setting of a normal heart rate. These conduction blocks can result in decreased cardiac output and the signs and symptoms of congestive heart failure, but can be well treated by cardiac pacing.

Modern cardiac pacing ([Kusumoto and Goldschlager, 2002](#)), either temporary or permanent, is achieved by a system of interconnected components consisting of (1) a pulse generator, which includes a power source and circuitry to initiate the electric stimulus and to sense cardiac electrical activity; (2) one or more electrically insulated conductors leading from the pulse generator to the heart, with a bipolar electrode at the distal end of each; and (3) a tissue, or blood and tissue, interface between electrode and adjacent myocardial cells. The pacemaker delivers a small current (2–4 mA) to the myocardium via the electrodes, resulting in depolarization and contraction of the heart.

Temporary pacing is most frequently used for patients with acute myocardial infarction that is complicated by cardiac conduction system disturbances that could progress to complete heart block. Leads for temporary cardiac pacing are generally directed transvenously into the apex of the right ventricle and the pulse generator is located outside the body. In the context of cardiac surgery when the epicardium is already exposed, temporary pacing is achieved by placing insulated wires with bare ends to the epicardial surfaces of the atria or ventricles with the leads emerging transthoracically from the anterior chest to permit easy withdrawal. Ultimately, the temporary pacemaker is either replaced by a permanent device or discontinued.

Permanent cardiac pacing involves long-term implantation of both pulse generator and electrode leads. The generator, usually made of a titanium alloy, is placed in a tissue pocket beneath the skin on the left anterior chest with the leads advanced transvenously through the left subclavian vein to terminate at the endocardial surface of the heart. The conducting elements are typically made of MP-35N (an alloy of nickel, cobalt, chromium, and molybdenum with excellent strength and corrosion resistance) in a composite with higher electrical conductance materials such as silver or stainless steel; these are typically insulated with an outer coating of silicone and/or urethane. The tips of the electrodes are typically placed within the right atrium and/or right ventricle depending on the pacing modality.

A single chamber pacemaker delivers a stimulus based on a programmed timing interval. The pacemaker also senses intrinsic cardiac activity and can be inhibited from providing unnecessary or inappropriate stimuli. This “demand” pacing is valuable in a patient whose problem is intermittent. A dual-chamber pacemaker with electrodes in both the atrium and ventricle delivers the sequential atrial and ventricular signals to approximate the timing of the normal heartbeat. This device also senses intrinsic atrial and ventricular depolarizations and delivers stimuli at the appropriate time to maintain proper synchrony of the chambers.

Patients with ventricular conduction delays such as left bundle branch block may suffer from heart failure due to dyssynchrony of ventricular contraction, where the right and left ventricles do not contract simultaneously. Cardiac resynchronization therapy via biventricular pacing is an intervention in which pacing electrodes are placed in the right atrium, right ventricle, and coronary sinus. The

coronary sinus electrode stimulates the lateral wall of the left ventricle to allow for simultaneous excitation of the right and left ventricles, and for more uniform contraction of the entire left ventricle. Cardiac resynchronization therapy has been shown to significantly improve cardiac function in these patients ([McAlister et al., 2007](#)).

Permanent implantable pacemakers are powered by lithium-iodide batteries with a finite lifespan of 5–8 years, requiring removal and reimplantation of a new device when the battery is exhausted. In fact, the first patient to receive an implantable pacemaker in 1958 required 22 different pulse generators until his death in 2001 at the age of 86. Improving battery technology to allow for longer lifespan would minimize the number of reimplantations that a patient would require and the complications that arise from these procedures.

The interface between the electrode and depolarizable myocardial tissue is of critical importance in the proper functioning of the pacemaker ([Fig. 2.5.2A.9D](#)). Typically, a layer of nonexcitable fibrous tissue induced by the electrode forms around the tip of the electrode, which is undesirable as it increases the strength of the threshold pacing stimulus required to initiate myocyte depolarization ([Fig. 2.5.2A.9E](#)). Strategies to reduce this fibrosis include improved lead designs, and the use of slow, local release of corticosteroids to minimize the thickness of fibrous tissue formed after lead implantation ([Mond and Grenz, 2004](#)). The practical point is that, if pulse generator output is not set sufficiently high in the early postimplantation phase, loss of pacing with potentially fatal consequences can result. By contrast, maintaining output at such high levels once thresholds have stabilized greatly shortens battery life. Thus pacemakers with adjustable variations in output have been developed.

An ideal endocardial pacing lead should provide stable fixation immediately from the time of implantation, achieve and maintain a minimal threshold for stimulation, maximize sensing, and function reliably for many years. Electrode fixation to the endocardium may be active or passive. In active fixation, the electrode is designed to grasp the endocardial surface to achieve immediate fixation at implantation. A very effective aid to passive fixation is the addition of projecting “tines,” or fins, in the region of the electrode tip. A different approach to improving fixation has been the development of electrodes with porous metal surfaces to foster tissue ingrowth. An endocardial pacemaker lead may require a special design if it is implanted at a particular site. One example is the J-shaped atrial lead, which is curved to facilitate placing the electrode tip in the right atrial appendage, inherently the most stable site for fixation.

“Leadless” pacemaker therapy ([Della Rocca et al., 2018](#)) is a new technology that has been introduced into clinical practice in the form of two novel devices: the Nanostim Leadless Pacing System (St. Jude Medical) and the Micra Transcatheter Pacing System (Medtronic, Inc.). These devices ([Fig. 2.5.2A.9F](#)) consist of a single capsule-like module that contains all of the functions of a traditional single-chamber pacemaker, but is implanted entirely within

the apical aspect of the right ventricle and attached to the interventricular septum via a primary fixation method involving a helical coil or tines. Implantation is performed percutaneously via a transvenous route under fluoroscopic guidance; the devices have a design feature at their proximal end such that they can be recaptured for repositioning during implantation or removal at a later date. The aim of these devices is to provide the same pacing function as a traditional transvenous pacemaker, but without the complications discussed later associated with a large subcutaneous generator pocket and associated long leads traversing the cardiac chambers and valves.

### Implantable Cardioverter-Defibrillators

The first implantable cardioverter defibrillator (ICD) was placed in 1980; currently, more than 100,000 ICDs are implanted annually in the United States. The goal of ICDs is to prevent sudden death in patients with certain life-threatening arrhythmias by resetting the heart's electrical activity and stimulating a normal cardiac rhythm. ICDs have been shown to revert sustained ventricular tachycardia (abnormally high ventricular rate) and ventricular fibrillation (uncoordinated electrical/myocardial activity) in multiple prospective clinical trials. Benefit in overall mortality has been well documented ([The Antiarrhythmics versus Implantable Defibrillators \(AVID\) Investigators, 1997](#)).

A transvenous ICD consists of similar components to a pacemaker, namely a pulse generator and leads for tachydysrhythmia detection and therapy. The pulse generator is a self-powered, self-contained computer with one or two 3.2 V lithium-silver vanadium oxide batteries used to power all components of the system, including aluminum electrolytic storage capacitors. The devices have a service life of 3–5 years, at which point they require removal and implantation of a new device. The lead is generally placed in the right ventricle through a transvenous approach. ICD leads typically contained several coaxial conducting elements that can sense as well as deliver an appropriate shock, each conducting element may be coated in an insulator such as polytetrafluoroethylene, with all of the elements encased within silicone and coated with an outer layer of urethane insulation. The ICD constantly monitors the ventricular rate, and when the rate exceeds a certain value, provides therapy. Current devices will initially provide a short burst of rapid ventricular pacing that terminates some types of ventricular tachyarrhythmias without providing a large shock. This approach can terminate up to 96% of episodes of ventricular tachycardia without the need for a shock. If this pacing fails to break the arrhythmia, the ICD delivers a shock of 10–30 J between the electrode in the right ventricle and the surface of the pulse generator to terminate the dysrhythmic episode. These devices also keep a running record of arrhythmias and treatment results. ICDs are indicated in patients at high risk for ventricular arrhythmias (primary prevention) and in patients who have already had an episode of aborted sudden cardiac death (secondary prevention).

In contrast to the transvenous ICD, a type of ICD termed a subcutaneous ICD (S-ICD) has been developed and is in clinical use for the detection and termination of malignant arrhythmias ([Willcox et al., 2016](#)). The S-ICD uses an extravascular lead that is implanted in the subcutaneous tissue parallel to the sternum just to the left of midline in most cases. The lead is connected to the generator, which is implanted in the midaxillary line on the left side of the thorax. The lead senses a “far field” signal from the electrical activity of the heart in a manner similar to a surface electrocardiogram, and the shock is delivered by the generator in the subcutaneous tissue overlying the heart in a way similar to an external defibrillator. The S-ICD is therefore not in contact with the heart and blood and is in a more stable mechanical environment, with the hope that some of the complications noted later will be reduced.

### Complications of Pacemakers and ICDs

These devices share many of the same complications, many of them requiring device removal and replacement. Like many cardiovascular devices, these are life-sustaining technologies and the implications of device failure can be fatal due to a lack of appropriate cardiac pacing (for pacemakers) or inability to sense or deliver appropriate therapy for a lethal arrhythmia (for ICDs). While normal device end-of-service from a depleted battery may not be technically considered a device malfunction, it certainly requires device replacement, and may happen prematurely due to increased fibrosis at the lead–tissue interface requiring a higher stimulus threshold. Failures of the hardware, including the battery/capacitor and charge circuit, connectors, and leads, are the most common device malfunctions, with software problems being less prevalent. Some mechanical failures include electrode dislodgment, lead fractures, electrode corrosion, and insulation failure ([Fig. 2.5.2A.9G](#)) ([Zeitler et al., 2015](#)). Complications of leads may be related to the body of the lead, as distinct from the lead–device pack interface or the electrodes. Several devices and components have been recalled in recent years for these modes of failure ([Amin and Ellenbogen, 2010](#)). Lead improvements over the years have included helical coil and multifilament designs to decrease electrical resistance and enhance flexibility and durability ([Haqqani and Mond, 2009](#)). In the past, many reports appeared on interference with pacemaker function by devices ranging from electric razors, toothbrushes, and microwave ovens at home to electrosurgical and diathermy apparatus in hospitals. Fortunately, recent generations of cardiac pacemakers have been greatly improved with regard to their resistance to electromagnetic interference.

Many complications relate to the interaction of the device biomaterials with the host tissue. These include infection, thrombosis and thromboembolism, myocardial penetration or perforation, pressure necrosis of the skin overlying the pulse generator, and migration or rotation of the pulse generator. Infection is a dreaded complication of implantable devices in general, and this is certainly true for

pacemakers and ICDs (Joy et al., 2017). The infection may originate in the subcutaneous pocket and track along the lead, which acts as a contaminated foreign body. Alternatively, it may occur by implantation of bacteria on traumatized endocardium or thrombus contiguous with the lead. The most common organisms responsible for these infections are coagulase-negative *Staphylococcus* species such as *S. epidermidis*. Septicemia may develop and septic pulmonary emboli may occur. The fundamental therapeutic principle in device-related endocarditis is treatment of the infection with antibiotics followed by removal of at least the lead and, when the pacemaker pocket is involved, the entire pacing system (Baddour et al., 2010).

ICDs contain more extensive hardware than pacemakers, and this may contribute an increased relative frequency of complications. Several additional considerations are specific to ICDs. The consequences of repeated defibrillations can cause the following effects: (1) direct effect of repeated discharges on the myocardium and vascular structures, and (2) possible thrombogenic potential of the indwelling intravascular electrodes. Another major complication of ICDs from the standpoint of the patient, other than the inability to sense or terminate an arrhythmia leading to sudden death, is an inappropriate shock. In addition to being startling and quite painful at the time of the shock, patients receiving multiple inappropriate shocks have been known to develop posttraumatic stress disorder symptoms.

As mentioned earlier, the leads are designed to optimize their interactions with the adjacent myocardium; this can be problematic when a complication arises in which the leads must be removed. Some leads can be removed by prolonged gentle traction, but many require additional tools and techniques to free them from the venous wall through which the body of the lead travels and from the myocardium to which they are often tenaciously adherent (Krainski et al., 2018). Recourse to cardiotomy with cardiopulmonary bypass may be needed if the lead is densely incarcerated in fibrous tissue.

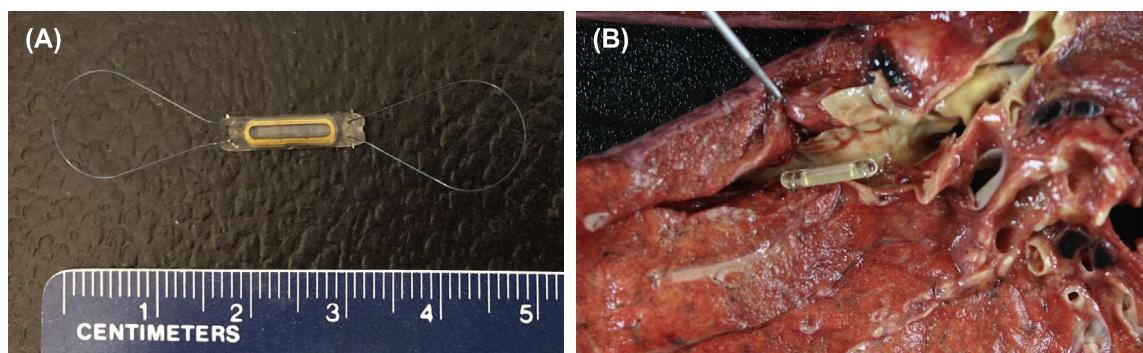
## Congestive Heart Failure

Congestive heart failure (Jessup and Brozena, 2003) is a deficiency of the pumping function of the heart and is an extremely common condition, affecting approximately 6.2

million Americans. Each year in the United States, congestive heart failure is the principal cause of death in 60,000 individuals, a contributing factor in over 280,000 deaths, and the primary discharge diagnosis in over 1.1 million hospitalizations, all increases over previous years. Cardiac transplantation is a potential solution for some of these patients (Mancini and Lietz, 2010). However, the increasing discrepancy between the number of acceptable donor hearts (only 2500 per year) and the number of patients who might benefit from cardiac transplantation (estimated at greater than 100,000 per year) has prompted efforts toward the development of mechanical devices to augment or replace cardiac function (Baughman and Jarcho, 2007; Boilson et al., 2010; Krishnamani et al., 2010).

Congestive heart failure is the final common pathway of many specific cardiac conditions, including valvular heart disease, coronary artery atherosclerosis with resultant ischemic heart disease, and diseases that affect the cardiac muscle directly (termed cardiomyopathies). Heart failure can occur precipitously, as in myocardial infarction or viral myocarditis, or it can be a slow, progressive worsening of exercise tolerance and shortness of breath over many months or years because of ongoing deterioration of the heart muscle. It can manifest itself in the postoperative period after both cardiac surgery (e.g., valve replacement, cardiac transplantation) and noncardiac surgery (e.g., abdominal aortic aneurysm repair).

When the left ventricle is failing of whatever etiology, blood backs up into the pulmonary circulation raising the pulmonary vascular resistance and increasing the pulmonary arterial pressure necessary to overcome that resistance. Hence, the pulmonary arterial pressure can be a surrogate marker of the degree of left heart failure in patients with chronic congestive heart failure. The CardioMEMS HF System (Micro-Electro-Mechanical HF System, Abbott Medical, Inc., Abbott Park, IL) provides hemodynamic information that can be used for the monitoring and management of heart failure (Ayyadurai et al., 2019). The device consists of a wireless sensor that is implanted in the distal pulmonary artery (Fig. 2.5.2A.10) generally via a catheter-based procedure. The sensor consists of a three-dimensional coil and pressure-sensitive capacitor encased between two wafers of fused silica, which is further encased in silicone.



**• Figure 2.5.2A.10** CardioMEMS device. (A) Unimplanted CardioMEMS pressure sensor. (B) In situ view of a CardioMEMS pressure sensor implanted in a branch of the pulmonary artery within the lung.

The coil electromagnetically couples the pressure-sensitive capacitor to the electronics system, allowing the measurement of the resonant frequency of the circuit without the need for an implanted battery. The resonant frequency is continuously converted to a pressure measurement, and the pressure waveform (including systolic, diastolic, and mean arterial pressures) and heart rate are transmitted to a receiver either in the hospital or the patient's home if they are ambulatory. The treating physician can access the data remotely and in real time to evaluate the patient and make any changes to the medical regimen. This strategy can be beneficial in certain patient groups or when used in structured programs (Dickinson et al., 2018).

As one might expect therefore, the natural history of heart failure depends on the cause and progression of the underlying disease process. For example, patients with heart failure after cardiac surgery (called postcardiotomy shock) often recover the vast majority of their cardiac function after a short period of time if they are otherwise sustained by mechanical circulatory support. In contrast, patients with dilated cardiomyopathy, one of the most common indications for cardiac transplantation, often need long-term mechanical support; studies have shown that at least 50% of such individuals would die in 3–5 years from their disease without it. One must take these clinical considerations into account when designing mechanical support systems, as different devices may best serve patients with different problems (DiGiorgi et al., 2003).

## Cardiopulmonary Bypass

First used in 1953 by Dr. John H. Gibbon, cardiopulmonary bypass devices pump blood external to the body and thereby permit complex cardiac surgical procedures to be done safely and effectively. Bypass machines are useful in extracorporeal membrane oxygenation (ECMO) to assist in the transport of oxygen and carbon dioxide for patients (especially neonates and infants) with pulmonary diseases such as the respiratory distress syndrome (Alpard and Zwischenberger, 2002).

The basic operating principles of the current heart–lung machines are quite straightforward and have changed little in the past half century. Deoxygenated blood returning from the systemic circulation into the right atrium is withdrawn by gravity siphon into a cardiotomy reservoir and is then pumped into an oxygenator. The most common type of oxygenator is a membrane oxygenator, where oxygen is passed through the tube side of a shell-and-tube-type device while the blood passes through the shell side. Oxygen and carbon dioxide are exchanged via diffusion through synthetic membranes (usually polypropylene or silicone) with high permeability to these respiratory gases. The oxygenated blood is then passed through a heat exchanger to adjust the temperature of the blood and the blood is returned to the systemic circulation via the aorta. At the beginning of the procedure, the patient is anticoagulated with heparin to reduce the risk of thrombosis within the device; as the patient is weaned from bypass, the anticoagulation can be quickly reversed by the use of a drug called protamine.

During an operation, the heat exchanger lowers the temperature of the blood and therefore the core body temperature, decreasing the metabolic requirements of the body and protecting the organs (including the heart) against ischemic damage. At the end of the operation, the blood can be warmed to normal physiologic temperature as the patient is weaned from the bypass machine.

A specially trained perfusionist controls the operation of the heart–lung machine, allowing the surgeon and anesthesiologist to concentrate on their respective tasks. This device therefore provides the function of both the heart (maintaining systemic blood flow and pressure) and the lungs (oxygenating blood and removing carbon dioxide), allowing the heart to be effectively stopped for delicate surgical procedures that would be more difficult or impossible to perform on a beating, moving heart. Many improvements to the original design of cardiopulmonary bypass machines have been made since their inception. One of the problems with the original heart–lung machines was the trauma that they would cause to the blood cells. Hemolysis of red blood cells would lead to functional anemia and loss of oxygen-carrying capacity of the blood; damage to platelets would lead to thrombocytopenia (low numbers of or dysfunctional platelets), resulting in bleeding problems. The problem of blood cell damage has been largely overcome with advanced pump designs and the use of the membrane oxygenators. Roller pumps and centrifugal pumps are commonly used because they cause a lesser degree of hemolysis and shear forces; it is important in the design of these pumps to determine the optimum balance between pumping function and hemolysis/shear stress to the formed blood elements. Bubble oxygenators, which directly pass bubbles of oxygen gas through the blood, cause more hemolysis, protein denaturation, and platelet dysfunction than membrane oxygenators and are currently less frequently used. In addition, newer devices allow blood that has escaped the circulation within the sterile operating field around the heart to be processed and returned to the patient, reducing the need for blood transfusion during the procedure.

Cardiopulmonary bypass can result in many pathophysiologic changes, including complement activation from the prolonged interaction of blood with synthetic surfaces, platelet and neutrophil activation and aggregation, changes in systemic vascular resistance, and expression of other pro-inflammatory mediators (Levy and Tanaka, 2003). When these changes are severe, the use of the heart–lung machine can result in complications, including confusion, renal insufficiency, pulmonary dysfunction, low-grade hepatic dysfunction, and increased susceptibility to infection. Together, these manifestations are termed the postperfusion syndrome. The last decade has seen development of mini extracorporeal circuit (MECC) cardiopulmonary bypass systems (Curtis et al., 2010) with a goal of providing cardiopulmonary bypass with a reduction in this harmful systemic inflammatory response. The MECC has a greatly reduced tubing length, smaller priming volumes, reduction in the blood–air interface, and fewer components than the standard bypass systems, and utilizes heparin-coated components and centrifugal blood

pumps. These systems show a reduction in postoperative cytokine levels, organ damage, postoperative complications, and the need for blood transfusions compared to standard circuits (Vohra et al., 2009).

## Percutaneous Mechanical Circulatory Support Devices

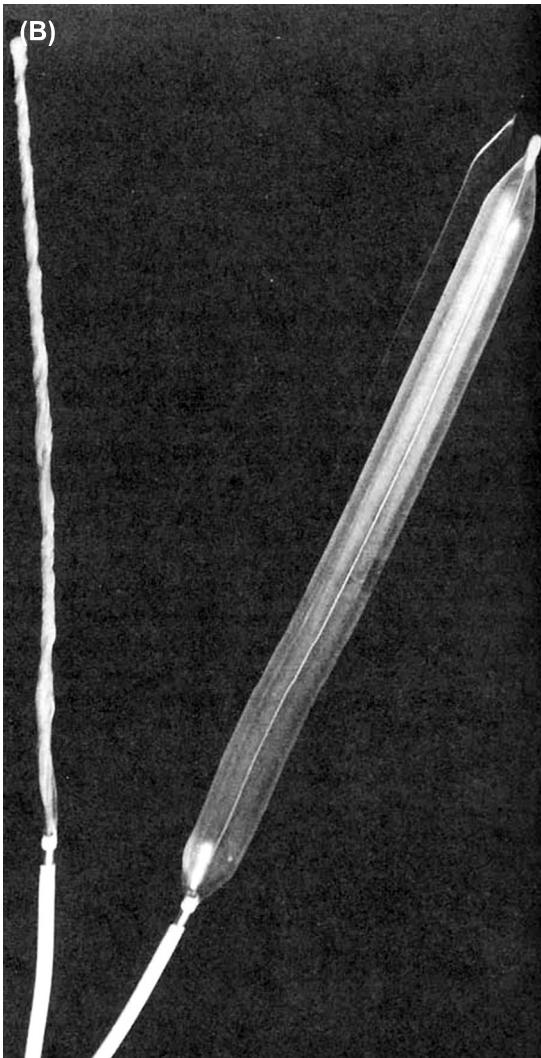
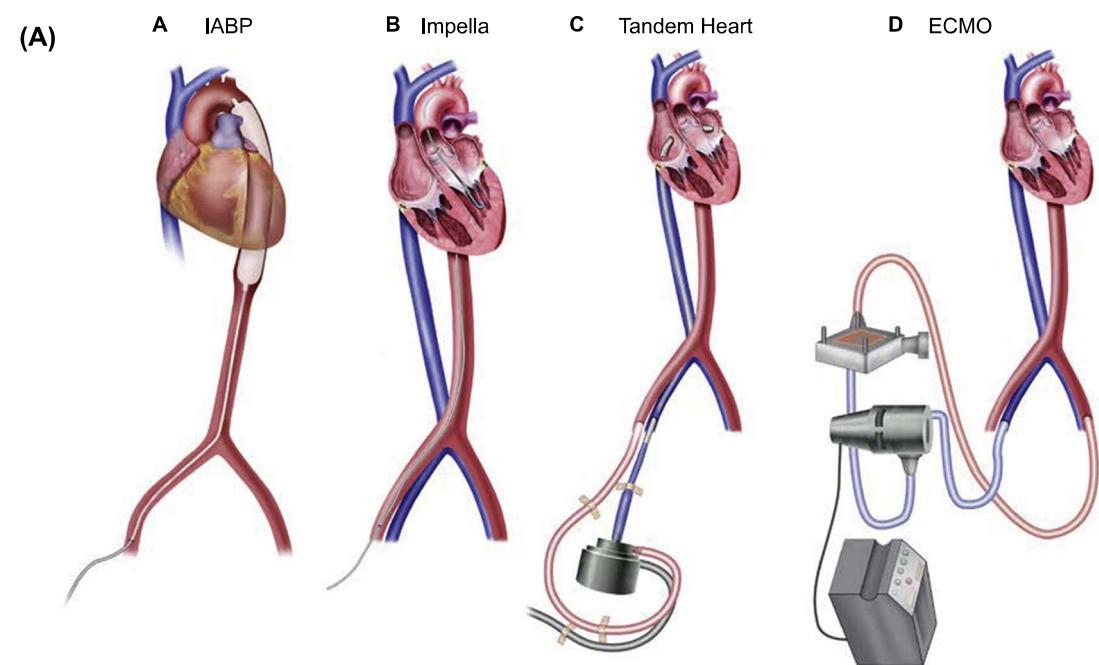
Percutaneous ventricular assist devices (VADs) (Mandawat and Rao, 2017; Miller et al., 2017) are used primarily for potentially reversible acute heart failure or cardiogenic shock, in which cardiac function is likely to recover with cardiac rest (e.g., postcardiotomy shock), or in cases of acute heart failure in which the patient needs to be stabilized quickly so that the possibilities for additional life-saving therapies (e.g., coronary artery bypass surgery, valve surgery, durable VAD placement, heart transplantation) can be assessed (“bridge-to decision”). The typical patient is critically ill with acute cardiogenic shock, mechanical complications of myocardial infarction such as ventricular septal or papillary muscle rupture, unrelenting ventricular arrhythmias, or advanced heart failure. Also, patients undergoing high-risk cardiac surgical procedures or percutaneous revascularization may benefit from the use of devices in the perioperative period to reduce myocardial oxygen demand. Percutaneous devices (Fig. 2.5.2A.11A) used in these situations include the intraaortic balloon pump (IABP), TandemHeart (Cardiac Assist, Inc., Pittsburgh, PA), Impella (ABIOMED, Inc., Danvers, MA), and ECMO.

Since the original use of the IABP in 1968 by Kantrowitz, the basic design and function of the current device has remained relatively similar during the ensuing decades. IABPs (Fig. 2.5.2A.11B) are catheter-based polyethylene or polyurethane balloons with volumes of 25–50 mL, although smaller devices are used in the pediatric population. Helium is most often used as the inflating gas; its low viscosity allows for rapid inflation and deflation and it is rapidly dissolved in the bloodstream in the event of inadvertent balloon rupture. IABPs (Baskett et al., 2002; De Sousa et al., 2010) are generally positioned under fluoroscopic guidance in the descending thoracic aorta after percutaneous insertion via the femoral artery. They are timed to inflate during diastole (ventricular filling) and deflate during systole (ventricular contraction) using the patient’s electrocardiogram or arterial pressure curve for synchronization; the devices discussed later do not have this requirement. This is termed counterpulsation (Trost and Hillis, 2006), which is out of phase with the patient’s heartbeat, and causes volume displacement of blood proximally and distally within the aorta. Several beneficial effects serve to improve cardiac function. Coronary blood flow (the majority of which occurs in diastole) is increased by the rise in diastolic pressure, delivering more oxygenated blood to the myocardium. In addition, left ventricular afterload (the pressure the myocardium must attain to pump blood into the aorta) is decreased, reducing the workload and therefore the oxygen requirement of the myocardium. The combination of these two hemodynamic

factors therefore improves the balance between myocardial oxygen supply and demand, and results in improved cardiac performance. The device also directly improves systemic circulation to a modest degree (approximately 10%). IABP therapy permits the heart to rest and recover enough function to support adequate circulation after the device has been removed, usually after only a few days. The major contraindications for IABP use include severe peripheral vascular disease, including aneurysms, aortic valve regurgitation, and aortic dissection (because of the need to thread the balloon through peripheral arteries and the aorta). Complications, which occurred in approximately 7% of patients with IABPs in a registry study, include limb ischemia from insertion site problems, bleeding, thrombosis with embolization, aortic dissection, balloon rupture, and sepsis.

The TandemHeart (Fig. 2.5.2A.11C) is a percutaneous VAD that supports the systemic circulation by withdrawing blood from the left atrium and reinjecting it into the abdominal aorta or iliac artery. The device has been commercially available since 2004. The pump, which sits in an extracorporeal location, is a continuous flow centrifugal pump that can provide up to 4–5 L/min of blood flow. The inflow cannula (usually 21-Fr in size) is typically inserted into a femoral vein, advanced into the right atrium and then pushed across the interatrial septum via transseptal puncture into the left atrium; when the device is withdrawn at the end of use, a small atrial septal defect remains. The outflow cannula (usually 15- to 17-Fr in size) is typically inserted into a femoral artery and advanced into the iliac artery or abdominal aorta. TandemHeart has been successfully used in a wide variety of clinical scenarios, including during high-risk percutaneous coronary interventions, bridge-to-recovery, bridge-to-decision, and bridge-to-transplant for patients with acute and advanced heart failure (Tempelhof et al., 2011; Kar et al., 2006). A modification of the TandemHeart allows it also to be used as a right VAD; a dual lumen cannula sits such that the inflow cannula of the device resides in the right atrium while the outflow cannula sits in the pulmonary artery distal to the pulmonic valve. One complication of the left-sided TandemHeart is the migration of the inflow cannula (meant to be in the left atrium) back into the right atrium. When this occurs, deoxygenated blood from the systemic venous return is drawn into the pump and returned into the systemic circulation, resulting in a right-to-left shunt. In addition, this steals blood from the right heart resulting in decreased pulmonary arterial flow leading to hypoxic respiratory failure. The most common complication with the TandemHeart is bleeding at the cannula insertion site(s), exacerbated by the need for anticoagulation to prevent pump thrombosis.

The Impella device (Fig. 2.5.2A.11D) is a continuous, non-pulsatile axial flow pump that employs an Archimedes-screw impeller that draws blood from the left ventricular cavity and expels blood into the ascending aorta distal to the aortic valve. There are currently three versions of the device for left-sided support. The Impella 2.5 provides 2.5 L/min of flow, the Impella CP provides 3.7 L/min, and the Impella 5.0 provides



**• Figure 2.5.2A.11** Percutaneous mechanical circulatory support devices. (A) The intraaortic balloon pump (IABP) is inserted through the femoral artery and resides within the aorta. The Impella is inserted through the femoral artery and passed retrograde across the aortic valve, with the pump inflow within the left ventricle and the outflow in the ascending aorta. The TandemHeart pump is extracorporeal, with the inflow cannula tip in the left atrium and the outflow in the iliac artery or abdominal aorta. Extracorporeal membrane oxygenation (ECMO) consists of both a pump and oxygenator, drawing deoxygenated blood from the systemic venous system and returning newly oxygenated blood to the systemic arterial circulation, similar in principle to cardiopulmonary bypass. (B) Percutaneous IABP. *Left*, balloon deflated for insertion. *Right*, balloon inflated. (C) Tandem Heart pump, with the central inflow port and peripheral outflow port. (D) Impella device with the inflow (yellow arrow) and outflow (red arrow) areas that would sit in the left ventricle and ascending aorta, respectively. The motor is housed in the gray area adjacent to the outflow area. ((B) Courtesy S. Volvek, Datascope Corp., Oakland, NJ.)

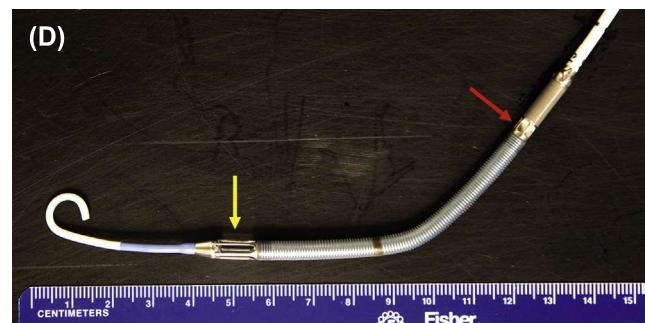


Figure 2.5.2A.11 cont'd

5.0 L/min. The device is typically inserted into the femoral or axillary artery and advanced retrograde across the aortic valve so the device inlet rests in the left ventricular cavity and the outlet sits distal to the aortic valve. While the first two devices can generally be inserted purely in a percutaneous fashion, the Impella 5.0 is large enough that it often requires a surgical cut down at the arterial insertion site. By virtue of its position in the left ventricle, the Impella unloads the left ventricular pressure as well as unloading volume, which is advantageous for reducing ventricular oxygen consumption and demand. In contrast, the left atrial inlet cannula position of the TandemHeart only unloads volume without significantly changing left ventricular pressure directly. Impella devices have been extensively used for patients undergoing high-risk percutaneous coronary interventions and for patients in cardiogenic shock secondary to acute myocardial infarction. They have also been investigated as a bridge-to-decision and even as a bridge-to-transplant in appropriate patients (Cheng et al., 2018). They are contraindicated in patients who have mechanical aortic valves or left ventricular thrombi. The more common complications of the device include device migration, thrombosis/thromboembolism, bleeding, hemolysis, and damage to left ventricular cardiac structures such as the aortic and mitral valves. The Impella RP is a similar device designed for right heart failure, which is inserted in the systemic venous circulation and sits such that the device inflow is in the right heart and the outflow is in the pulmonary artery distal to the pulmonic valve.

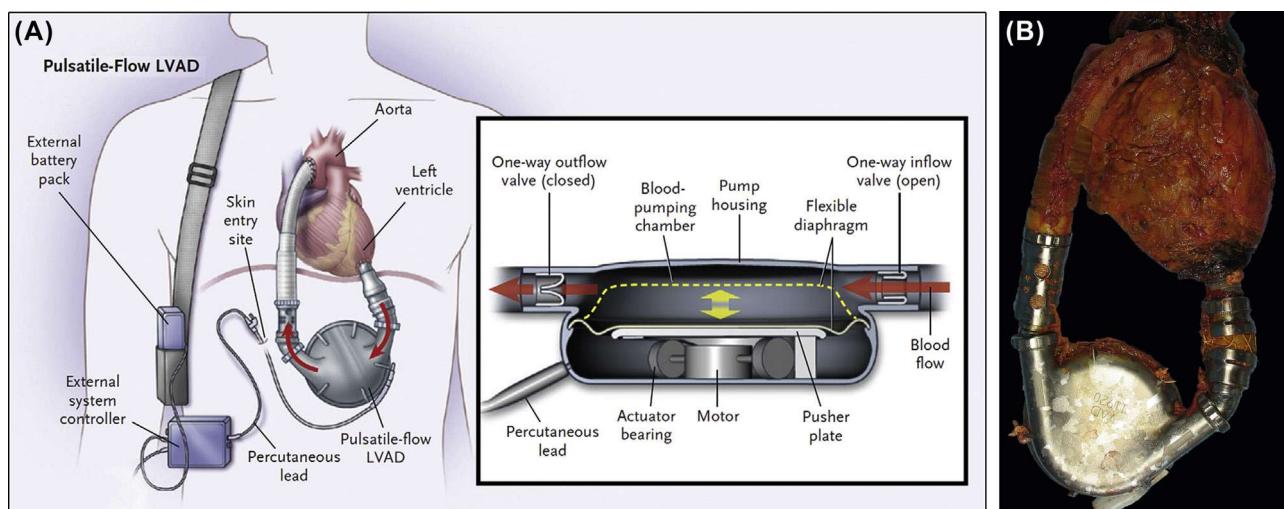
ECMO, in contrast to the other percutaneous devices, provides the functions of both the heart (blood pressure and flow) and lungs (gas exchange) and is increasingly being used for patients with both acute cardiovascular and pulmonary diseases. The ECMO circuit is analogous to cardiopulmonary bypass in the operating room, but in a system that can be utilized at the bedside. The usual configuration is venoarterial (VA-ECMO) where systemic venous blood is removed from the patient, and passed through a continuous flow centrifugal pump, a heat exchanger, and a membrane oxygenator to provide full biventricular support and gas exchange. Cannulation can occur peripherally and percutaneously using the femoral vein and artery, or can use a surgical approach with cannulation of the right atrium and aorta in an open procedure. Just as with cardiopulmonary bypass, it is critical to have an experienced multidisciplinary team ensuring adequate functioning of the device and monitoring of the patient.

## Durable Ventricular Assist Devices and Total Artificial Hearts

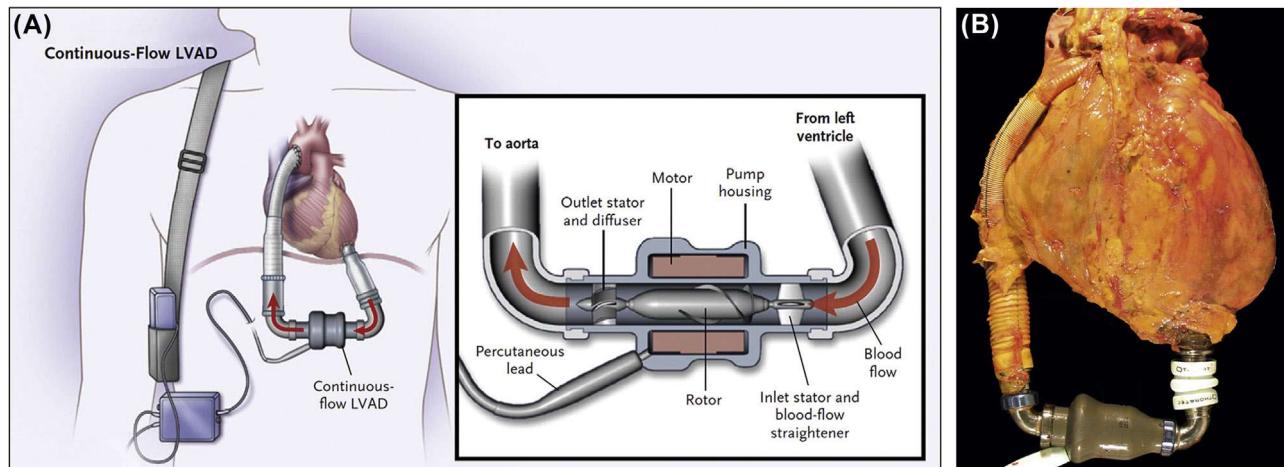
Durable VADs, first successfully employed by DeBakey in 1963, can replace ventricular function for extended periods, in contrast to the short-term duration of cardiopulmonary bypass, IABP, and percutaneous VADs. Durable VADs are currently used primarily in three settings: (1) for end-stage cardiac failure not likely to recover and where mechanical support will provide a “bridge-to-transplantation”; (2) for long-term cardiac support for patients with end-stage congestive heart failure that are not transplant candidates (“destination therapy”) (Christiansen et al., 2008); and (3) for chronic congestive heart failure where the unloading of the left ventricle may induce myocardial changes that might lead to normalization of cardiac function and eventually allow device removal (“bridge-to-recovery”). Research in this latter area focuses on the mechanisms of cardiac recovery, identification of patients who could achieve recovery, and specifics such as the timing and duration of therapy (Maybaum et al., 2008; Birks, 2010).

The first generation of durable VADs used as bridge-to-transplant or destination therapy (Hunt and Frazier, 1998) were large, pulsatile systems, with the inflow cannula of the device generally connected to the left ventricular apex and the outflow cannula connected to the ascending aorta. The pump itself would either be implanted in the peritoneal cavity with a driveline traversing the skin to provide power and controller functions, or would remain extracorporeal with the inflow and outflow cannulae each traversing the skin. Examples of first-generation pulsatile left ventricular assist devices (LVADs) included Thoratec HeartMate XVE (Fig. 2.5.2A.12) (Rose et al., 2001) and Novacor Ventricular Assist System (Dagenais et al., 2001); the Thoratec PVAD (Farrar et al., 1990) is an example of a paracorporeal VAD. These devices generally consisted of a flexible polymer pumping bladder or diaphragm actuated by a pusher plate to allow filling and emptying of the pumping chamber. Valves on the inflow and outflow aspect of the pump ensured unidirectional flow of blood. These devices were very large and posed many challenges; nevertheless, these devices were critical in bridging patients to transplant from the 1980s into the mid-2000s. While the Thoratec PVAD is still occasionally used, the other devices are obsolete.

The second generation of durable VADs consists of implantable continuous axial flow devices, where the long



• **Figure 2.5.2A.12** (A) Diagram of the HeartMate XVE pulsatile ventricular assist device. (B) Photograph of HeartMate XVE and heart after removal from a patient at autopsy. ((A) Reproduced with permission from Slaughter, M.S., Rogers, J.G., Milano, C.A., Russell, S.D., Conte, J.V., Feldman, D., Sun, B., Tatooles, A.J., Delgado, R.M., Long, J.W., Wozniak, T.C., Ghumman, W., Farrar, D.J., Frazier, O.H., 2009. Advanced heart failure treated with continuous-flow left ventricular assist device. *N. Engl. J. Med.* 361, 2241–2251.)

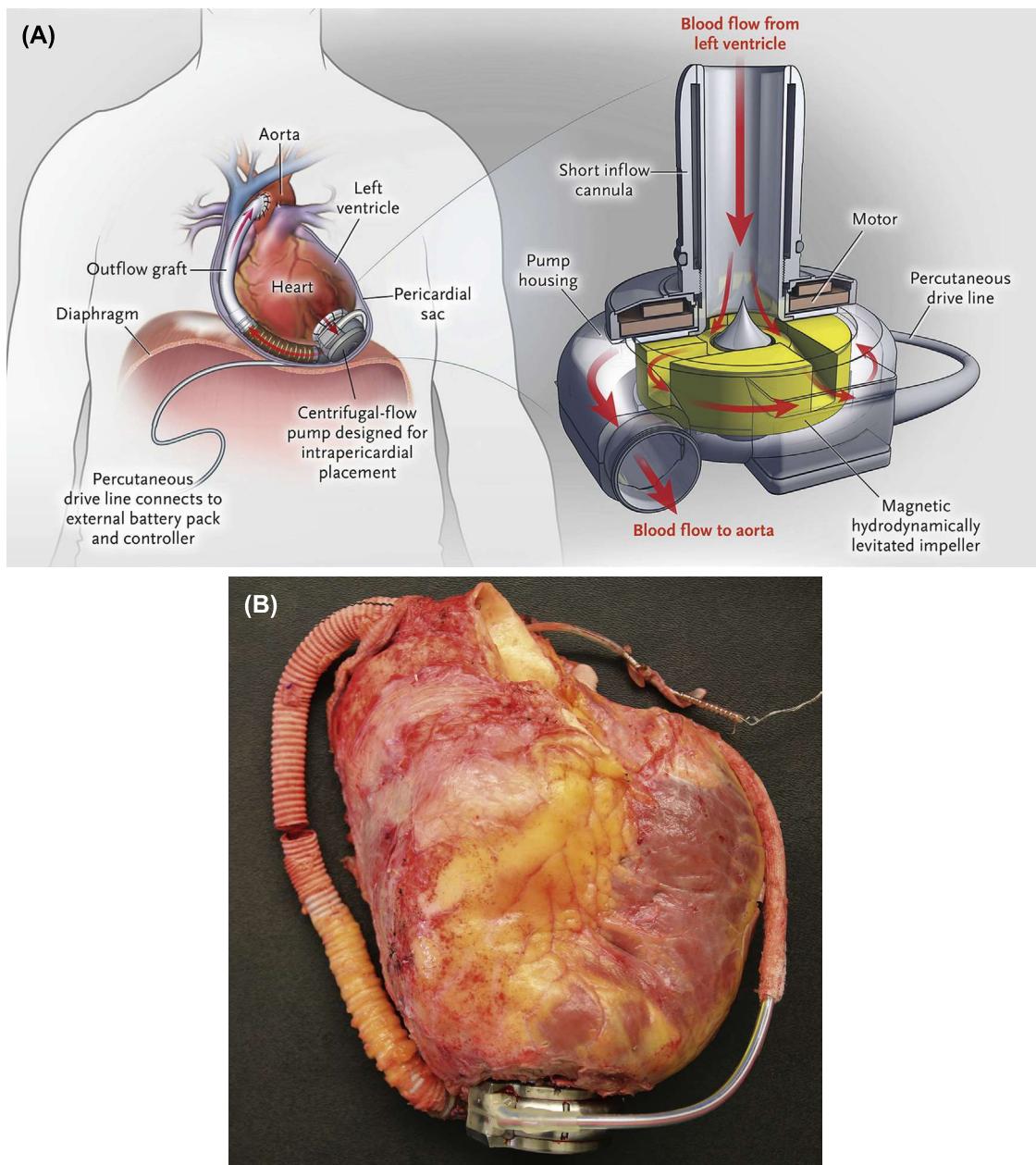


• **Figure 2.5.2A.13** (A) Diagram of the HeartMate II continuous axial flow ventricular assist device. (B) Photograph of HeartMate II and heart after removal from patient at autopsy. ((A) Reproduced with permission from Slaughter, M.S., Rogers, J.G., Milano, C.A., Russell, S.D., Conte, J.V., Feldman, D., Sun, B., Tatooles, A.J., Delgado, R.M., Long, J.W., Wozniak, T.C., Ghumman, W., Farrar, D.J., Frazier, O.H., 2009. Advanced heart failure treated with continuous-flow left ventricular assist device. *N. Engl. J. Med.* 361, 2241–2251.)

axis of the impeller is parallel to the direction of blood flow. Examples of such devices include Thoratec HeartMate II (Fig. 2.5.2A.13) (Slaughter et al., 2009), BerlinHeart INCOR (Schmid et al., 2005) (pumps reside within the peritoneal cavity), and Jarvik 2000 FlowMaker (Sorensen et al., 2012) (the pump is intraventricular). These second-generation devices are connected in much the same way as the implantable first-generation devices but are much smaller, making implantation easier and allowing smaller patients to receive them; they are also more durable than the first-generation devices. Since these are all continuous flow devices, the pumps themselves do not impart pulsatility to the blood resulting in reduced pulse pressure for the patient;

this reduction of pulse pressure does not seem to have significant clinical effects. Data demonstrate lower complication rates and improved outcomes over this time, especially with newer continuous flow LVADs as compared to the first-generation pulsatile devices (Kirklin et al., 2017).

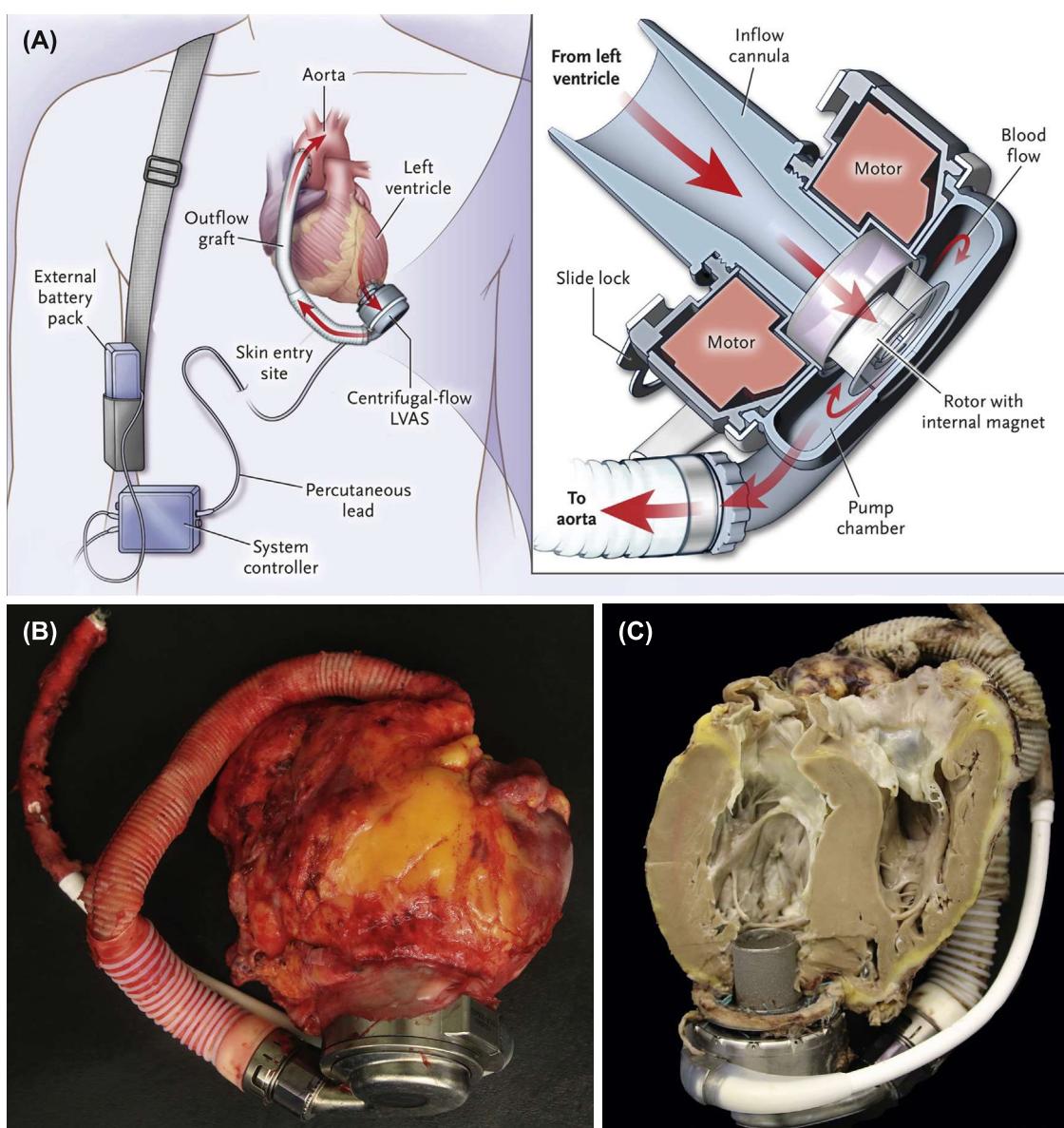
The third generation of VADs consists of implantable continuous centrifugal flow devices, where the impeller creates a centrifugal force to add kinetic energy to the flowing blood. Examples of such devices include HeartWare HVAD (Aaronson et al., 2012), Thoratec HeartMate 3 (Schmitto et al., 2015), and Evaheart LVAS (Saito et al., 2014). The use of these devices is accelerating, with a respective decline in the use of the second-generation VADs.



**• Figure 2.5.2A.14** (A) Diagram of the HeartWare Ventricular Assist Device (HVAD), a continuous flow centrifugal pump. (B) Photograph of HVAD and heart after surgical explantation from a patient who was bridged to cardiac transplantation with this device. ((A) Reproduced with permission from Rogers, J.G., Pagani, F.D., Tatooles, A.J., Bhat, G., Slaughter, M.S., Birks, E.J., Boyce, S.W., Najjar, S.S., Jeevanandam, V., Anderson, A.S., Gregoric, I.D., Mallidi, H., Leadley, K., Aaronson, K.D., Frazier, O.H., Milano, C.A., 2017. Intraperitoneal left ventricular assist device for advanced heart failure. *N. Engl. J. Med.* 376, 451–460.)

The HeartWare Ventricular Assist Device (HVAD, Medtronic, Inc., Minneapolis, MN) was the first implantable third-generation centrifugal flow device available in the United States, with important design differences from the commercially available axial flow devices (Larose et al., 2010); it received CE Mark approval in 2008 followed by FDA approval in 2012. The pump is smaller and resides directly on the epicardial surface of the left ventricle (Fig. 2.5.2A.14), with the inflow cannula residing within the left ventricular cavity. The rotor produces continuous, centrifugal flow with a magnetically levitated impeller rather than

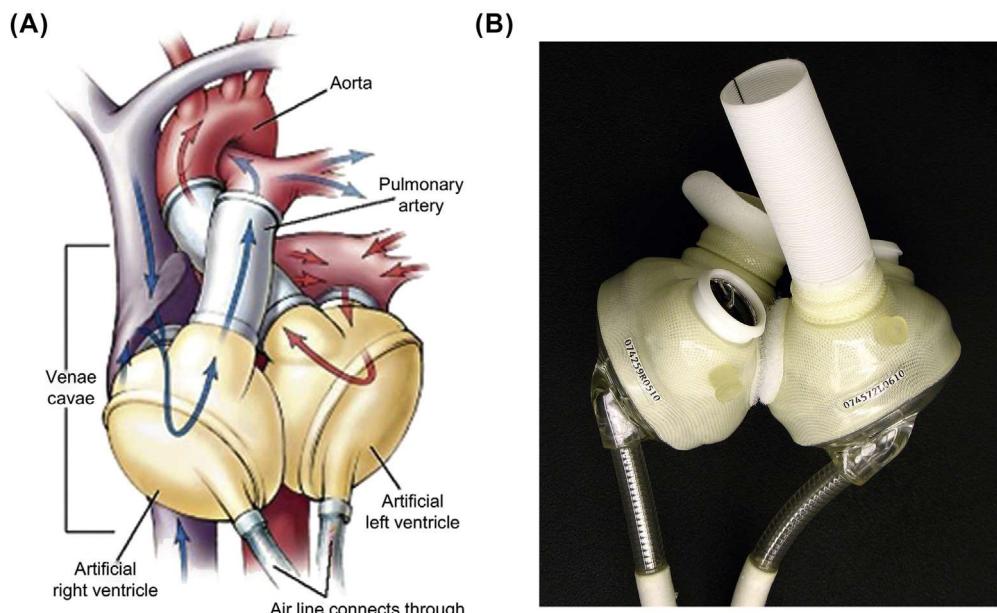
the axial flow system of the Thoratec HeartMate II, for example, which requires inflow and outflow bearings to support and align the impeller. The smaller pump size and driveline, intrathoracic positioning, and flow characteristics of the HVAD are thought to be advantageous in reducing common device complications such as infection, thrombosis, and bleeding. The HVAD ADVANCE trial demonstrated noninferiority (91% patient survival at 6 months) to other commercially available devices in a bridge-to-transplant setting, and there are longer follow-up data in a postmarket registry (Streuber et al., 2014). The original HVAD inflow



**• Figure 2.5.2A.15** (A) Diagram of the HeartMate 3 Ventricular Assist Device, a continuous flow centrifugal pump. (B and C) Photograph of HeartMate 3 and heart after surgical explantation from a patient who was bridged to cardiac transplantation with this device. ((A) Reproduced with permission from Mehra, M.R., Naka, Y., Uriel, N., Goldstein, D.J., Cleveland, J.C., Colombo, P.C., Walsh, M.N., Milano, C.A., Patel, C.B., Jorde, U.P., Pagani, F.D., Aaronson, K.D., Dean, D.A., McCants, K., Itoh, A., Ewald, G.A., Horstmannshof, D., Long, J.W., Salerno, C., 2017. A fully magnetically levitated circulatory pump for advanced heart failure. *N. Engl. J. Med.* 376, 440–450.)

cannula had a smooth, polished titanium outer surface, which raised concerns about the increased risk of cerebrovascular accidents secondary to device-related thromboemboli (Najjar et al., 2014). A change in the HVAD inflow cannula design was therefore implemented in an attempt to promote nonthrombotic passivating tissue overgrowth by replacing the smooth, polished titanium surface with one incorporating a collar of sintered titanium microspheres (Soltani S, 2015). However, this created a discontinuity at the smooth-sintered interface on the outer aspect of the inflow cannula that appears to serve as a nidus for thrombus formation (Glass et al., 2019). The HeartMate 3 (Fig. 2.5.2A.15) is the latest third-generation centrifugal flow pump with a fully magnetically levitated motor along with active magnetic

mounting (Chatterjee et al., 2018). It was first implanted in humans in 2014 by a group in Germany (Schmitto et al., 2015). The motor incorporates a contactless bearing technology and consists of the rotor with passive magnets for drive and bearing, the stator with electromagnetic coils for drive and levitation, along with distance sensors and a microcontroller. This pump is approximately one-third the size of the HeartMate I and is implanted in the pericardial space rather than in the abdominal cavity. The inflow cannula is fully sintered and resides within the left ventricular chamber, with the outflow graft anastomosed to the ascending aorta. It can deliver up to 10 L/min of flow, and can also generate an “artificial pulse” by periodically increasing and decreasing the pump speed mimicking a pulse rate of



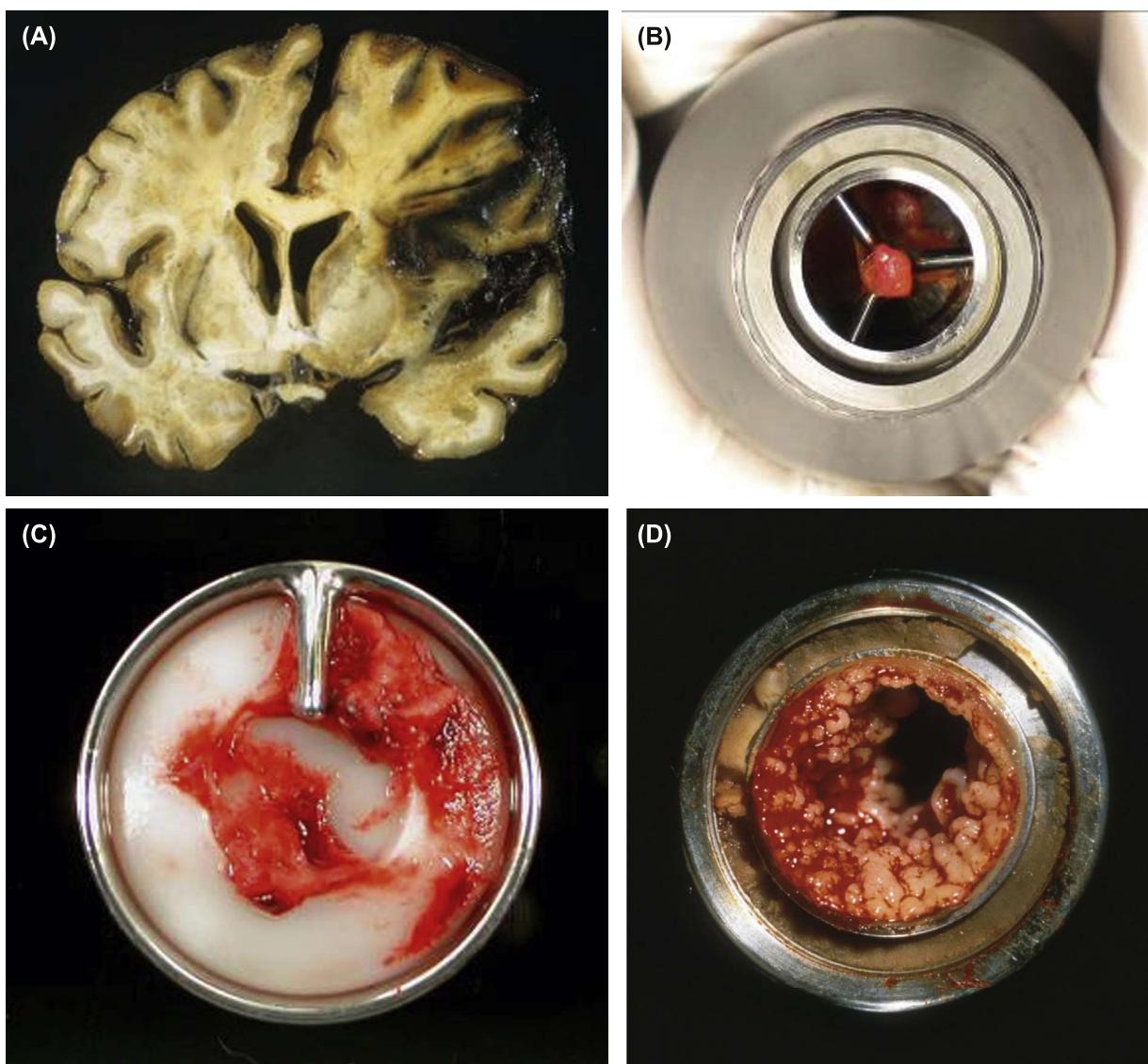
**• Figure 2.5.2A.16** (A) Diagram of the SynCardia Total Artificial Heart. (B) Photograph of an unimplanted SynCardia Total Artificial Heart. ((A) Reproduced with permission from Copeland, J.G., Smith, R.G., Arabia, F.A., Nolan, P.E., Sethi, G.K., Tsau, P.H., McClellan, D., Slepian, M.J., 2004. Cardiac replacement with a total artificial heart as a bridge to transplantation. *N. Engl. J. Med.* 351, 859–867.)

30 beats per minute. The MOMENTUM 3 clinical trial was designed to compare the centrifugal flow HeartMate 3 with the axial flow HeartMate II in patients with advanced heart failure. The HeartMate 3 showed lower rates of pump thrombosis, stroke, and reoperation to remove or replace a malfunctioning pump compared to the HeartMate II at 2-year follow-up (Mehra et al., 2018).

In contrast to VADs where the native heart remains in place, a total artificial heart is composed of two pumping chambers that together replace the entire heart and provide both right and left ventricular function, analogous to heart transplantation (Fig. 2.5.2A.16). The SynCardia Total Artificial Heart (SynCardia Systems, Inc.; Tucson, AZ) has been implanted worldwide in more than 1000 patients with biventricular heart disease (Copeland et al., 2003; Copeland et al., 2012). The device was approved by the FDA in 2004 and has proven to be an effective and reliable device for successful bridge-to-transplant. The clinical indications for implantation have included biventricular failure, left ventricular failure with prior mechanical heart valves, left ventricular failure with severe anatomical damage (ventricular septal defect, AV disruption), intractable malignant arrhythmias, massive ventricular thrombus, cardiac allograft failure, hypertrophic or restrictive cardiomyopathy, and complex congenital heart disease. The device is an implantable, pneumatically driven pulsatile pair of pumps consisting of polyurethane ventricles, whose inflows are anastomosed to the left and right atria and whose outflows are anastomosed to the ascending aorta and pulmonary artery after complete removal of the native cardiac ventricles and all four valves. Medtronic-Hall mechanical valves on the inflow and outflow aspects of the pump ensure unidirectional flow.

Systemic infection and thromboembolic or hemorrhagic events have been reported as the most common complications that prevent successful bridge-to-transplant.

The major complications of cardiac assist devices are hemorrhage, thrombosis/thromboembolism, infection, interactions with host tissue, and device component failure, including the pump and peripheral electrical systems (Fig. 2.5.2A.17). Hemorrhage continues to be a problem in device recipients, although the risk of major hemorrhage has been decreasing with improved devices, therapies, patient selection, and surgical methods. Many factors predispose to perioperative hemorrhage, including (1) anticoagulation therapy and its management along with coagulopathy secondary to liver dysfunction and poor nutritional status, (2) contact of the blood with the device resulting in intrinsic platelet dysfunction and acquired von Willebrand disease, and (3) the extensive nature of the required surgery. Nonthrombogenic blood-contacting surfaces are essential for a clinically useful cardiac assist device or artificial heart. Indeed, thromboembolism occurred in most patients having long-term implantation of the Jarvik-7 artificial heart and is a major design consideration for current devices. In the absence of adequate anticoagulation and despite the development of minimally thrombogenic blood-contacting surfaces and appropriate blood flow characteristics, thrombi can form in areas of disturbed blood flow such as connections of conduits and other components to each other and to the natural heart. The current generation of continuous flow LVADs is carefully designed to minimize thrombosis, but oral anticoagulation is still required. Pump thrombosis in the continuous axial flow HeartMate II LVAD at the inflow bearing was one of the major sources of morbidity and mortality for patients with this device. Thrombi also may form outside the



**• Figure 2.5.2A.17** Complications of cardiac assist devices. (A) Hemorrhage into the brain in a patient with a left ventricular assist device (LVAD). (B) Thrombus on the inflow flow straightener and inflow bearing of the impeller of the HeartMate II LVAD. (C) Thrombus on the inflow valve of a Thoratec PVAD. (D) Fungal infection in LVAD outflow graft. ((A) and (C)) Reproduced with permission from Padera, R.F., 2008. Pathology of ventricular assist devices. In: McManus, B.M., Braunwald, E. (Eds.), *Atlas of Cardiovascular Pathology for the Clinician*, second ed. Current Medicine Group LLC, Philadelphia. (D) Reproduced by permission from Schoen, F.J., Edwards, W.D., 2001. Pathology of cardiovascular interventions. In: Silver, M.D., Gotlieb, A.I., Schoen, F.J. (Eds.), *Cardiovascular Pathology*, third ed. Churchill Livingstone, New York.)

LVAD, often in association with crevices and voids as in the HeartWare HVAD discussed earlier, and in areas of disturbed blood flow such as near connections of conduits and other components to the native heart. These thrombi can detach and lead to catastrophic embolic events such as ischemic stroke. Accounting for significant morbidity and mortality following the prolonged use of cardiac assist devices, infection can occur either within the device or associated with percutaneous drive lines (Padera, 2006). Susceptibility to infection is potentiated not only by the usual prosthesis-associated factors, but also by the multisystem organ damage from the underlying disease, the periprosthetic culture medium provided by postoperative hemorrhage, and by prolonged hospitalization with the associated risk of nosocomial infections. Assist device-associated infections are often resistant to antibiotic therapy and host defenses,

but are generally considered not an absolute contraindication to subsequent cardiac transplantation. Novel device designs, including alternative sites for driveline placement and the elimination of the driveline altogether with transcutaneous energy transmission technology, may play a role in further decreasing infection.

## Atrial Septal Defects and Other Intracardiac Defects

In prenatal life, circulation is different than it is in postnatal life (Schoen and Mitchell, 2015). The lungs of the fetus are not providing gas exchange, so oxygenation of fetal blood is provided via the placenta and maternal circulation. This

requires two important shunts that need to close immediately after birth to separate the circulation into the pulmonary and the systemic arms. The foramen ovale, a hole in the fetal intraatrial septum, allows oxygenated blood returning to the right atrium from the placenta to preferentially pass into the left atrium. This blood passes through the mitral valve into the left ventricle and is pumped out through the aorta into the systemic circulation. The ductus arteriosus, present between the pulmonary artery and aorta, allows deoxygenated blood pumped from the right ventricle to bypass the lungs and directly reenter the systemic circulation, as the prenatal pulmonary circulation has a high vascular resistance (because of the nonexpanded lungs). After birth, these functional shunts should close to completely separate the right and left circulations; failure to do so results in a patent foramen ovale (PFO) or patent ductus arteriosus (PDA) that can allow inappropriate shunting of blood in the postnatal circulation. In addition, atrial septal defects (ASDs) or ventricular septal defects (VSDs) can also result from abnormal formation of the atrial septum or ventricular septum. While these defects can be closed via an open surgical procedure (sutures and/or fabric patches for PFO, ASD, or VSD, ligation for PDA), efforts have been made to allow closure of these defects using a minimally invasive approach. The decision to close a PFO, ASD, VSD, or PDA depends on the size of the shunt and the symptoms of the patient; the choice of technique (surgical vs. percutaneous) depends on the anatomy and structure of the defect.

## Closure Devices

The first catheter-based closure of a PDA was performed in 1967 by Porstmann using an Ivalon plug to occlude flow through the ductus arteriosus. Of the many PDA closure devices that have been developed over the years, most are metal-based devices that work by causing thrombosis of the PDA with subsequent organization and fibrosis, permanently preventing flow through the residual ductus arteriosus. Three of the more commonly used devices are the Gianturco coil (stainless-steel coil containing polyester fibers to promote thrombosis), the Amplatzer Duct Occluder (ADO, a conical device consisting of Nitinol wires and a polyester fiber patch to promote thrombosis and tissue integration), and the next-generation ADO II (Barateau et al., 2014).

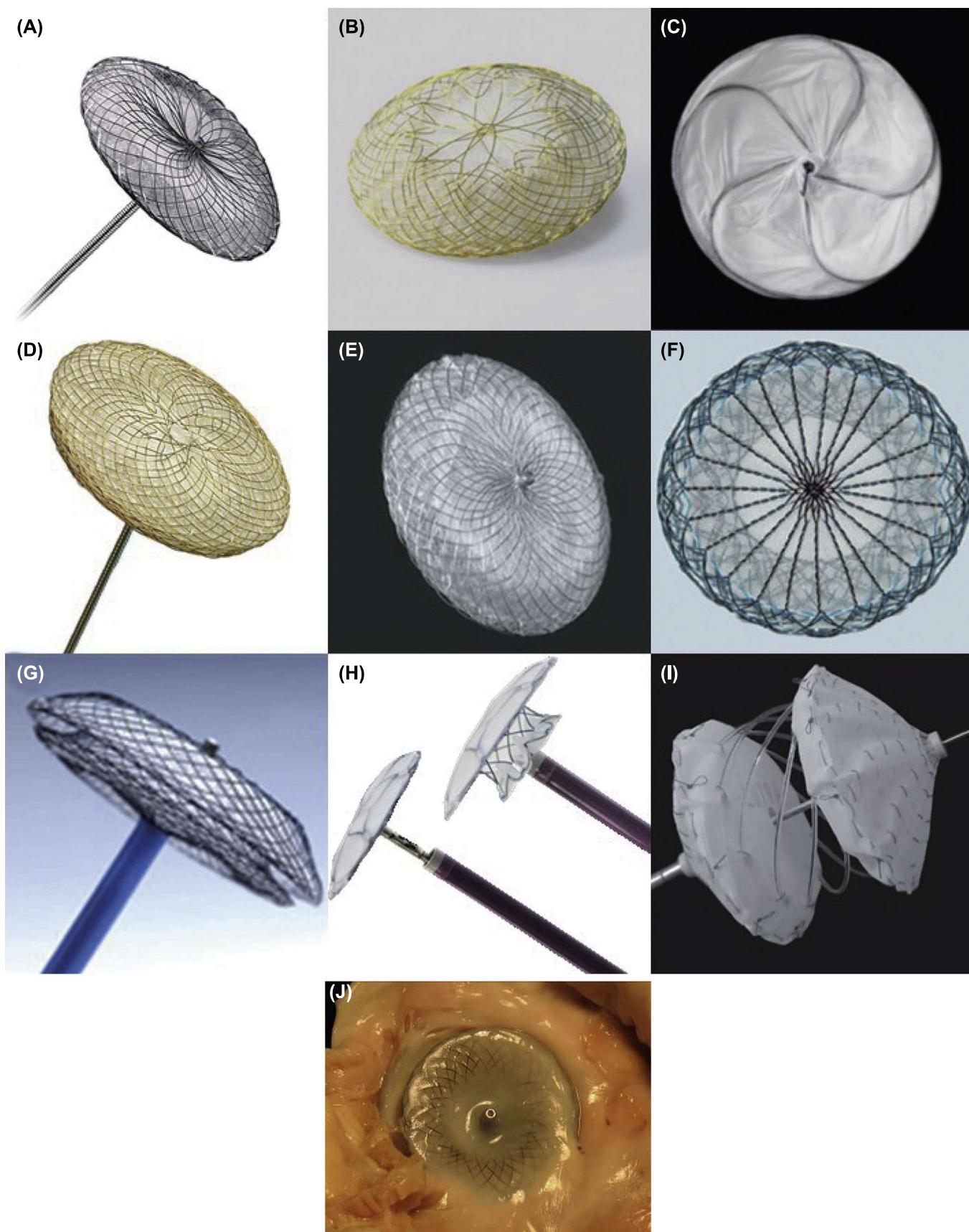
Mills and King reported the first transcatheter closure of an ASD in 1976 using a double umbrella device that covered the opening from both the right and left atrial sides. Their occlusion device consisted of a skeleton of expanded polytetrafluoroethylene (ePTFE)-coated wire supporting an occluder of Dacron fabric delivered through a catheter. Improvements over the years include better device fixation methods and smaller caliber introducers. Several designs (Fig. 2.5.2A.18) of PFO/ASD closure devices are currently in use (Jung and Choi, 2018). The Amplatzer device (St. Jude Medical, St. Paul, MN) is a self-centering device that consists of double Nitinol disks filled with polyester patches

connected by a small waist; the waist sits within the defect to connect the disks, which sit on either side of and are selected to be larger than the defect. The Gore Cardioform Septal Occluder (W.L. Gore and Associates, Flagstaff, AZ) is a nonself-centering device composed of a platinum-filled Nitinol wire framework, which is covered by an ePTFE patch designed to promote endothelialization. Advantages of nonsurgical closure devices such as these include shorter hospital stay, more rapid recovery, and no residual thoracotomy scar. With the experience gained in the transcatheter closure of PFOs and ASDs, this interventional technology is being extended to the closure of some VSDs, particularly in patients thought to be poor operative risks.

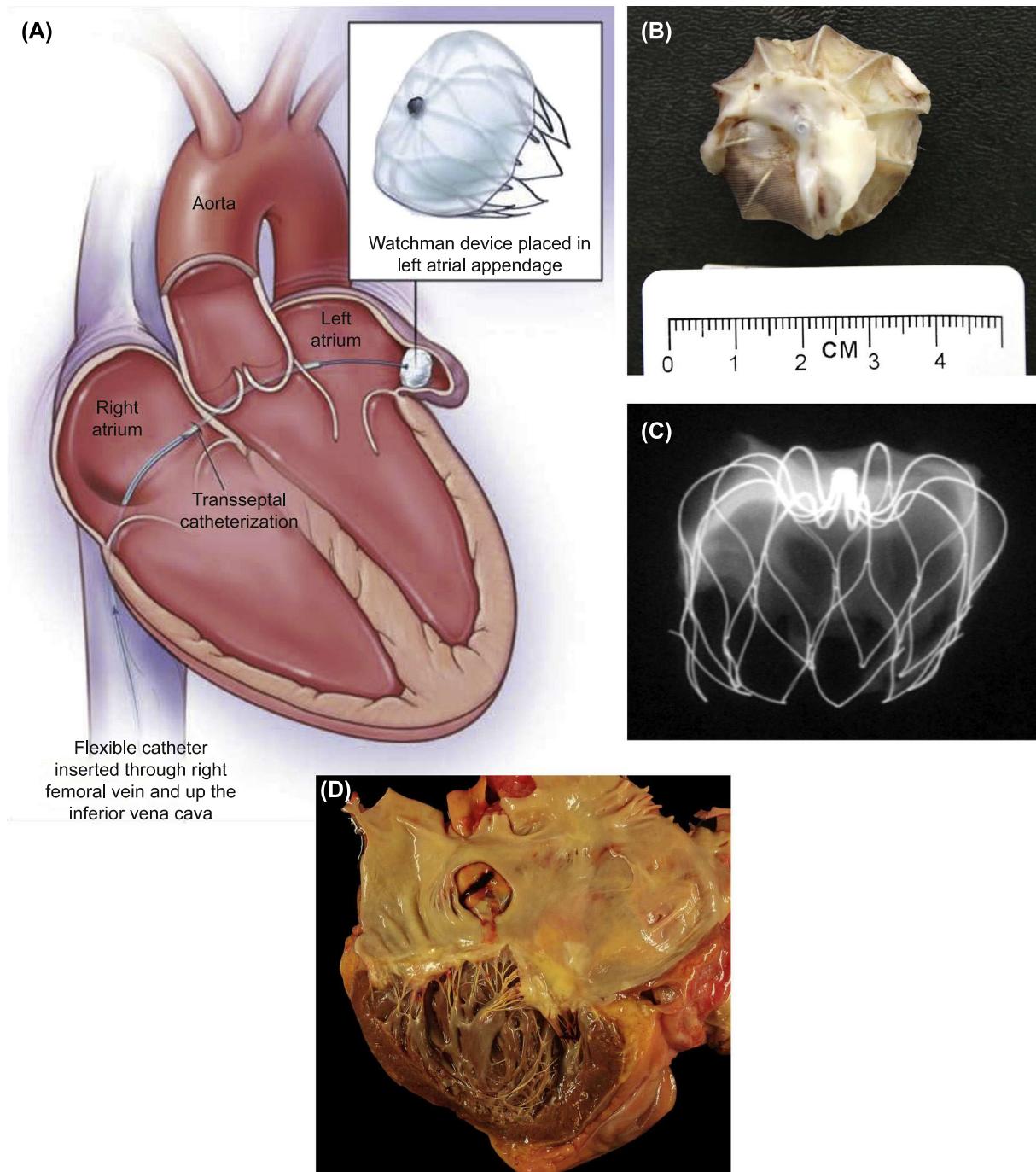
Several types of complications have been reported for closure devices. The most straightforward is the failure to fully close the defect resulting in residual shunting. Erosion of the device through the interatrial septum occurs in some patients with perforation and device embolization; this is thought to be secondary to the specific anatomy of the defect, but the stiffness of the device may also play a role. Inadequate fixation of the device within the defect or a device-defect size mismatch can also result in device embolization. Closure devices are effective in closing defects at least in part via thrombosis; if the thrombosis extends beyond the defect on the device, thromboemboli may result. Fractures of various device components, air embolism at the time of device deployment, infection, and development of new arrhythmias have also been reported. A number of devices are in development, with the trends being defect-specific design and minimization of the amount of foreign material left in the patient, including the use of biodegradable components (O'Byrne and Levi, 2019).

## Atrial Fibrillation

AF affects more than 3 million individuals in the United States, making it the most common cardiac arrhythmia. Instead of orderly atrial contraction initiated by the SA node, rapid disorganized electrical activity in the atria causes these upper chambers of the heart to quiver or fibrillate resulting in poor contractile function and irregular flow within the chamber. As would be predicted by Virchow's triad, thrombosis may occur due to these flow abnormalities within the atria, especially within the atrial appendage. Atrial appendage thrombi are an important source of thromboemboli, explaining why patients with AF are at a fivefold greater risk for embolic stroke than individuals in sinus rhythm. Anticoagulation is effective in reducing the risk of atrial thrombosis and stroke, but this therapy has many drawbacks, including a narrow therapeutic window, variability in metabolism of the drug, interactions with other drugs and metabolites, need for frequent monitoring by blood drawing, poor patient compliance, and, most importantly, the risk of life-threatening bleeding. These side effects are reduced in a class of drugs called nonvitamin K antagonist oral anticoagulants when compared to the established vitamin K antagonists such as warfarin (Granger et al., 2011), but there is still a



**Figure 2.5.2A.18** Closure devices for intraatrial septal defects. (A) Amplatzer Septal Occluder; (B) Occlutech Figulla Flex II device; (C) Gore Cardioform Septal Occluder; (D) Cocoon Septal Occluder; (E) CeraFlex ASD device; (F) Nit Occlud ASD-R device; (G) Cardi-O-Fix Septal Occluder; (H) Ultracept II ASD Occluder; (I) Carag Bioresorbable Septal Occluder; (J) Amplatzer Septal Occluder after 2 years with fibrous tissue overgrowth. ((A–I) Reproduced with permission from Jung, S.Y., Choi, J.Y., 2018. Transcatheter closure of atrial septal defect: principles and available devices. *J. Thorac. Dis.*, 10, S2909–S2922.)



**• Figure 2.5.2A.19** The Watchman left atrial appendage occluder device. (A) Diagrammatic. (B) Photograph of Watchman device showing coverage by host tissue. (C) Specimen radiograph of Watchman device showing metallic framework. (D) Photograph of heart at autopsy with Watchman device successfully occluding the left atrial appendage. (A) Reproduced with permission from Maisel, W.H., 2009. Left atrial appendage occlusion – closure or just the beginning? *N. Engl. J. Med.* 360, 2601–2603.)

bleeding risk with these newer medications. An approach for reducing the risk of thromboembolic stroke in patients with AF is to remove or ligate the left atrial appendage, first proposed in the 1930s and first performed in 1949 via a surgical approach. This approach is typically used when a patient is undergoing a concomitant cardiac surgical procedure such as valve replacement or bypass surgery.

### Left Atrial Appendage Occlusion Devices

Nonsurgical device-based approaches to close the left atrial appendage have been developed, including several devices that can be deployed percutaneously to occlude the opening to the appendage and isolate it from the blood in the left atrium (Pacha et al., 2019). The Watchman (Fig. 2.5.2A.19)

left atrial appendage system (Boston Scientific, Marlborough, MA) is an FDA-approved, percutaneously deployed parachute-shaped device consisting of a Nitinol cage with a polyethylene terephthalate membrane on its surface and fixation barbs along the perimeter, which allows it to anchor in the atrial appendage. This device has been shown to be noninferior to standard warfarin therapy for prevention of embolic stroke and systemic embolization, and superior to warfarin for prevention of cardiovascular death and hemorrhagic stroke in recent clinical trials (Holmes et al., 2009; Reddy et al., 2017). The Amplatzer Amulet (St. Jude Medical, Minneapolis, MN) device is another current generation percutaneously deployed left atrial occlusion device that is currently in clinical trials (Kleinecke et al., 2017) prior to FDA approval. The Atriclip Device System (Atricure, Inc., West Chester, OH) is an occlusion device applied on the epicardial surface at the base of the left atrial appendage to close the entrance to the left atrial appendage by external compression (Alawadi et al., 2011). The device consists of two parallel rigid titanium tubes with elastic Nitinol springs that hold the device closed.

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