41 The Use of Isolated Heart Models and Anatomical Specimens as Means to Enhance the Design and Testing of Cardiac Devices

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Abstract

In recent years, the use of perfusion-fixed cadaveric specimens and isolated heart models has helped to develop an improved understanding of the device-tissue interface and has also contributed to the rapid evolution of surgically and percutaneously delivered cardiac therapies. This chapter describes a novel series of techniques utilized within the Visible Heart® laboratory by engineers, scientists, and anatomists to visualize and analyze the heart and assess potential repair or replacement therapies. The study of reanimated large mammalian hearts (including human hearts) and specially prepared anatomical specimens, using various clinical and nonclinical imaging modalities, has provided feedback for design engineers and clinicians that seek to develop and/or employ cardiac therapies for patients with acquired or congenital heart disease.

Keywords

Isolated heart model • Cardiac device design and development • Human cardiac anatomy • Reanimated heart

41.1 Introduction

A detailed and comprehensive understanding of human cardiac anatomy remains a crucial component of cardiovascular medical practice, research, and cardiac device design and development [1, 2]. The successful deployment and performance of a particular cardiac device is continually impacted by the ability of the device to conform and adapt to the changing anatomical landscape of the heart, as well as to anatomical variations that may exist in a given patient. In other words, successful device design and development requires a well-developed understanding of the relevant cardiovascular anatomies (in relation to both vascular approaches and within the heart itself) at every stage of the process [3–5].

The study of fixed and reanimated human hearts, using the various methodologies described here, has provided for novel insights as to the details of human cardiac anatomy. For almost two decades, the Visible Heart® methodologies have provided a unique perspective on functional cardiac anatomy. By reanimating human hearts not deemed viable for transplant, we have been able to visualize the beating heart using a variety of imaging modalities, including: (1) endoscopes placed directly within the various heart chambers and/or within the large diameter vessels, (2) echocardiography, (3) fluoroscopy, (4) magnetic resonance imaging (MRI), (5) infrared thermography, and/or (6) high-speed cameras. This database of images and videos exemplifies the large degree of variability that exists in human cardiac anatomy (from both a static and functional perspective) [6]. Additionally, such imaging techniques allow for visualization of the anatomical changes that occur as a result of various

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pathologies and/or those that may occur following the deployment of devices within the heart.

Recent advances in intracardiac interventions have increased the need for a greater understanding of the anatomical complexities of the heart prior to the respective procedure. Further, as clinicians become more comfortable with the delivery of novel devices within beating hearts, the already widespread utilization of percutaneous technologies such as coronary stenting and transcatheter valve replacement will continue to intensify. This is highlighted today by the highly competitive field of transcatheter aortic valve implants, where competing designs attempt to provide the most effective treatment for the patient in a package that enables physicians to comfortably and reliably administer the therapy. Consequently, it has become more critical than ever for device developers to have a thorough understanding of: (1) the variations of cardiac anatomy that will present in the patient populations they treat and (2) the results they obtain from in vitro and in vivo testing of potential therapies.

This chapter will discuss the use of anatomical specimens and isolated heart preparations as important methodologies to provide the required educational foundation needed for the fields of cardiac device design, development, and deployment.

41.2 Anatomical Specimens and Static Imaging

Throughout history, anatomists such as Galen, Vesalius, da Vinci, and more recently Hunter, Gray, and Netter have recreated their knowledge gained from the dissection of animal and human cadavers in elegant treatises. However, with the advent of high-resolution noninvasive imaging in the past century, our understanding of the functional internal anatomy of the body has progressed even more rapidly. This accelerated growth of knowledge has led to the proposed utilization of attitudinally correct nomenclature, in an attempt to ensure that anatomists, surgeons, radiologists, cardiologists, echocardiographers, and biomedical engineers are able to communicate using common anatomical terms (see Chap. 2) [7].

Combined with these advances in our understanding of cardiac anatomy, there has also been progress in the preparation of anatomical specimens for research. The ancient Egyptians, as part of the ritual preparation of their deceased kings for burial, preserved bodies through the technique of embalming. However, until the discovery of glutaraldehyde and formaldehyde in the mid-nineteenth century, human cadavers used for medical dissections were not typically preserved in embalming solutions with anatomists relying on the cooler temperatures of winter to extend their dissection times. The introduction of powerful chemical preservation techniques extended the period of time anatomists could study a particular specimen and also increased the integration of anatomical classes in medical teaching. However, the fixation of the heart within the body as prepared for an anatomical study preserves the myocardium in a state of rigor, usually with the various heart chambers collapsed and potentially full of clotted materials (blood). In 1978, researchers at the Mayo Clinic (Rochester, MN, USA) adapted a formalin pressure perfusion system used in the study of pulmonary disorders to prepare the heart for anatomical investigations [8, 9]. However, the technique was time consuming and did not become more commonly used until Thomas and Davies reported the use of a simple apparatus to allow for the perfusion fixation of fresh cardiac specimens [10]. This technique has since been used extensively for the preparation of cardiac specimens by cardiac morphologists such as Robert Anderson [11] and has been adopted by the Visible Heart® laboratory as the preferred method of preparation for the cardiac specimens within the Visible Heart® library [5].

41.3 The Visible Heart® Library

Our laboratory has the privilege to obtain fresh human heart specimens for educational and research purposes from: (1) organ donors whose hearts are not deemed viable for transplantation and are donated for research (via LifeSource, the Upper Midwest Organ Procurement Organization, St. Paul, MN, USA) and (2) bodies donated to the University of Minnesota's Anatomy Bequest Program. After excision, these fresh, unfixed specimens are subsequently cleaned and perfusion fixed in 10 % buffered formalin, by attaching the cannulated great vessels of each heart to a pressure head of approximately 50 mmHg. This technique, modified from Thomas and Davies [10] and described by Anderson et al. [5], fixes the hearts in an approximation of the end-diastolic state, providing a unique insight into the anatomical dimensions of a given specimen. Figure 41.1 demonstrates various images that can be acquired from these specimens and shows some of the cardiac pathologies (those depicted here are diseases of the cardiac valves) that can be subsequently visualized [12].

To date, our library of more than 350 hearts of various disease states continues to provide researchers with the ability to investigate how the cardiac anatomy may change/remodel under specific pathologies. In addition to anatomical investigations, these specimens can be employed to provide information as to how a specific device will fit the cardiac anatomies of the intended patient population, or how a delivery system will navigate through the chambers and

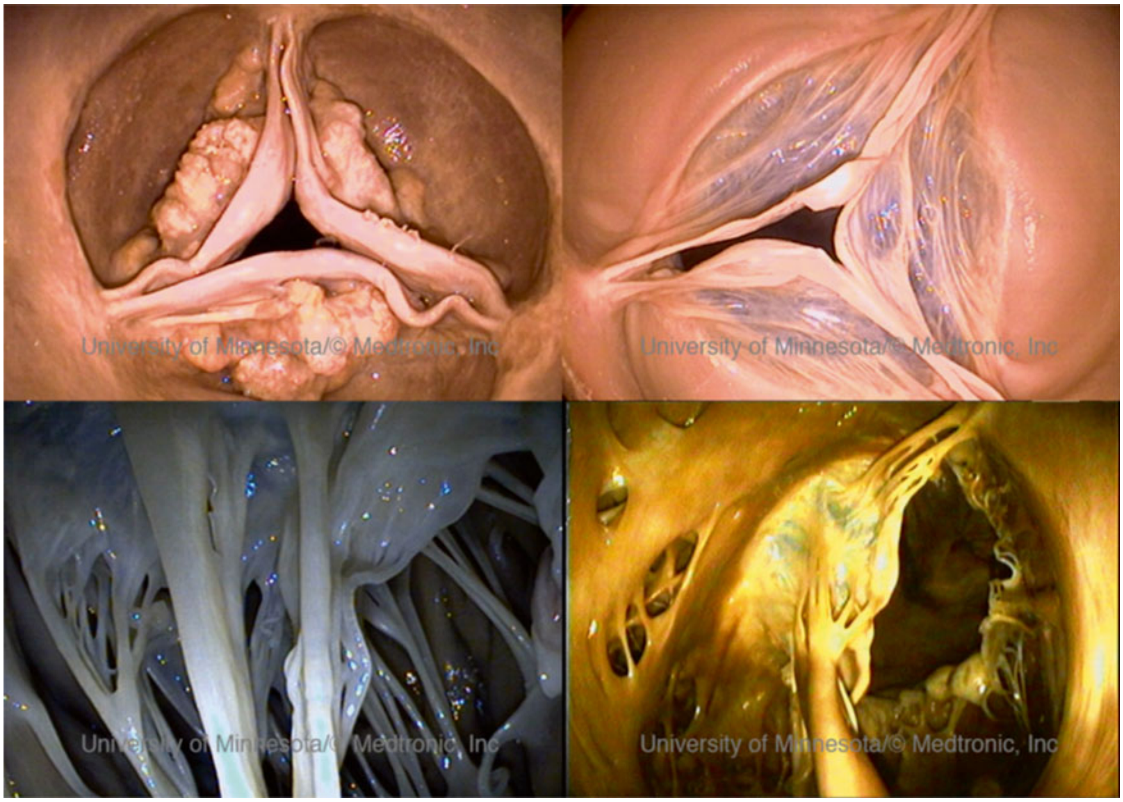

Fig. 41.1 Images from perfusion-fixed hearts from the Visible Heart® laboratory's library: (1) calcified aortic valve (*upper left panel*), (2) pulmonary valve (*upper right panel*), (3) subvalvular apparatus of the mitral valve (*lower left panel*), and (4) tricuspid valve from the right ventricle (*lower right panel*). Modified from The Atlas of Human Cardiac Anatomy [12]

vasculature of the heart. Such resources have allowed for the placement of multiple prototype devices and rapid comparison of how specific devices interact with the surrounding cardiac anatomies in a variety of human specimens [13, 14]. This information is critical in the development process, as it allows for engineers to highlight challenges regarding implantation of the device or the navigation of the delivery system that may have been overlooked in bench top testing.

Fresh cadaver hearts received by the Visible Heart® laboratory are documented at each stage of the acquisition process to record global anatomical changes during the fixation process, such as tissue weight and overall dimensions. Images of the fresh preparation, the resulting fixed specimen, and the nondestructive imaging of a sample specimen from the library (adapted from the Atlas of Human Cardiac Anatomy [12]) can be seen in Fig. 41.2.

Recent advances in high-resolution noninvasive cardiac imaging have fostered extensive work in the in vivo analyses of anatomical variations from patient to patient using a variety of imaging modalities:

1. Cardiac ultrasound (e.g., transthoracic, transesophageal, intracardiac, 2D, 3D, and/or 4D) [15]
2. Computed tomography (CT) [16]
3. Multi-slice computed tomography [17]
4. Magnetic resonance imaging (MRI, e.g., 1.5 T, 3 T, or greater) [18]

Nondestructive imaging of specimens from the Visible Heart® library via ultrasound, CT, and MRI has been used to collate a digital database of these hearts for educational and research purposes. The perfusion-fixed specimens are prepared by suspending them in a gel medium, allowing for a full complement of multimodal imaging to be performed on the hearts without changing the orientation [19]. Obtaining high-resolution images has allowed for detailed analyses of cardiac anatomies for a variety of normal and pathologic specimens; this spectrum of imaging is considered not possible with available clinical imaging protocols. For example, the analysis of fiber orientations of specimens obtained from patients in end-stage heart failure, using diffusion tensor MRI [20], provided critical insight into the remodeling of the ventricular tissue in patients with chronic heart failure. In addition, it has been possible to compare the ability of different imaging modalities to assess the anatomical characteristics of specific cardiac pathologies such as aortic stenosis, thus building on the work of other researchers [21, 22]. For additional imaging of such specimens, see Chaps. 6, 7, and 8.

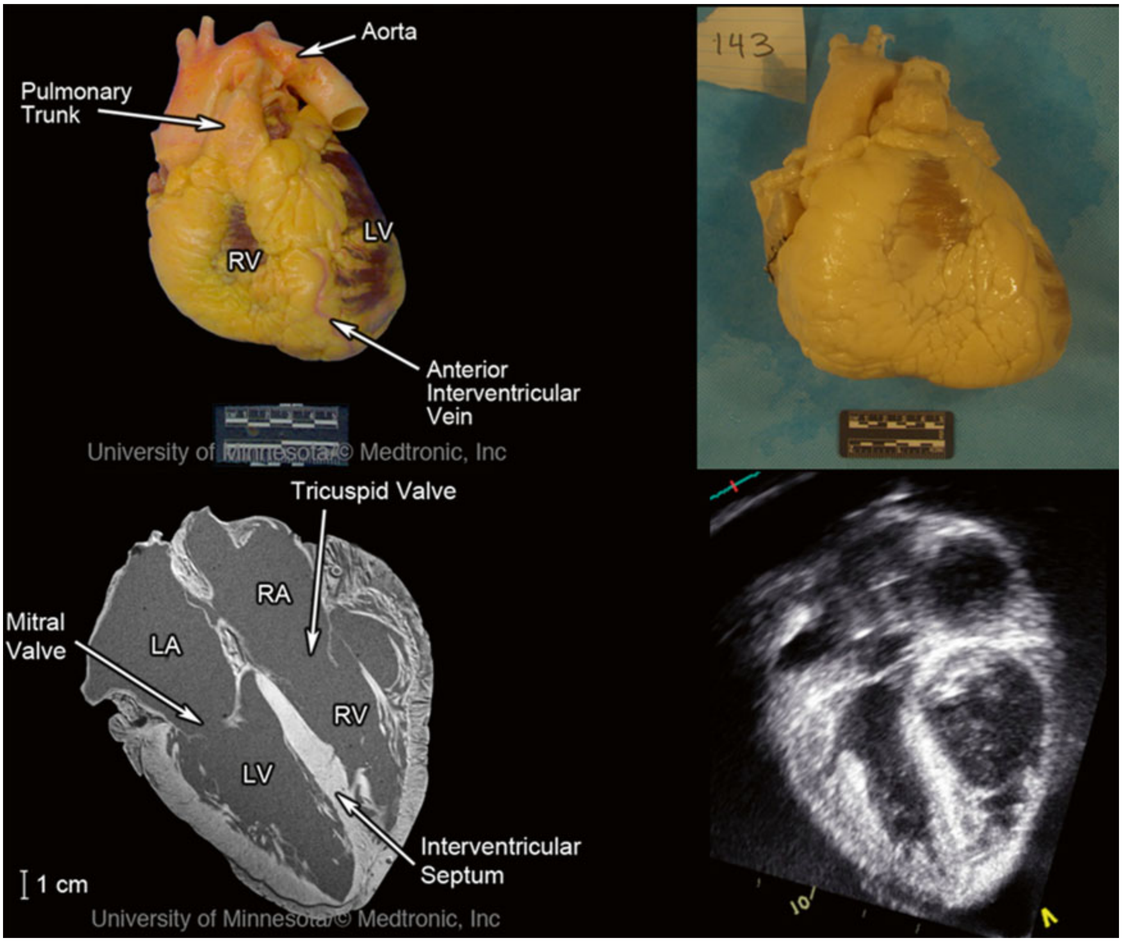

Fig. 41.2 Images of a heart received by the Visible Heart® library and imaged fresh (*upper left panel*), after perfusion fixation (*upper right panel*), and scanned in a 3 T Siemens MRI scanner (*bottom left panel*) and GE Vivid I ultrasound (*lower right panel*) in the four-chamber long-axis view. Modified from The Atlas of Human Cardiac Anatomy [12]

41.4 In Vitro Isolated Heart Models

A comprehensive understanding of the cardiac anatomy provides device designers with fundamental information regarding the anatomical dimensions and variations of the environment into which the device or therapy will be delivered. However, these static human heart specimens do not address the complications surrounding the delivery and function of a device or therapy in a beating heart. Before embarking upon complex and expensive chronic animal testing protocols which are required to prove the efficacy of novel cardiac devices, there is exceptional value in testing in reanimated beating heart models. Our laboratory at the University of Minnesota has reanimated over 1500 large mammalian hearts (canine, ovine, swine, mini-pigs, and human) for such studies in the last 15 years. There have been several other academic institutions and private companies that have developed in vitro large mammalian heart models, with many groups effectively developing systems based upon the mechanical reanimation of cadaveric large mammalian hearts. For example, Richards et al. were able to consistently and reliably quantify mitral regurgitation across a range of severity in explanted porcine hearts and investigate the efficacy of various repair techniques [23]. Further, two other groups have succeeded in studying the electrophysiology of explanted human hearts by sustaining the heart with a pressurized coronary flow of oxygen saturated salt solution via Langendorff perfusion [24, 25]. However, it should be noted that the true *reanimation* of large mammalian hearts (whereby the heart functions independently of any mechanical or electrical assistance) has only been achieved by a small number of research groups. Araki et al. (Nagoya University, Japan) reported that they were able to complete optical and hemodynamic analyses of cardiac valves in reanimated swine hearts [26]. Most recently, Weger et al. at the Leiden University Medical Center, Netherlands, have monitored transcatheter valve implantations in reanimated swine hearts

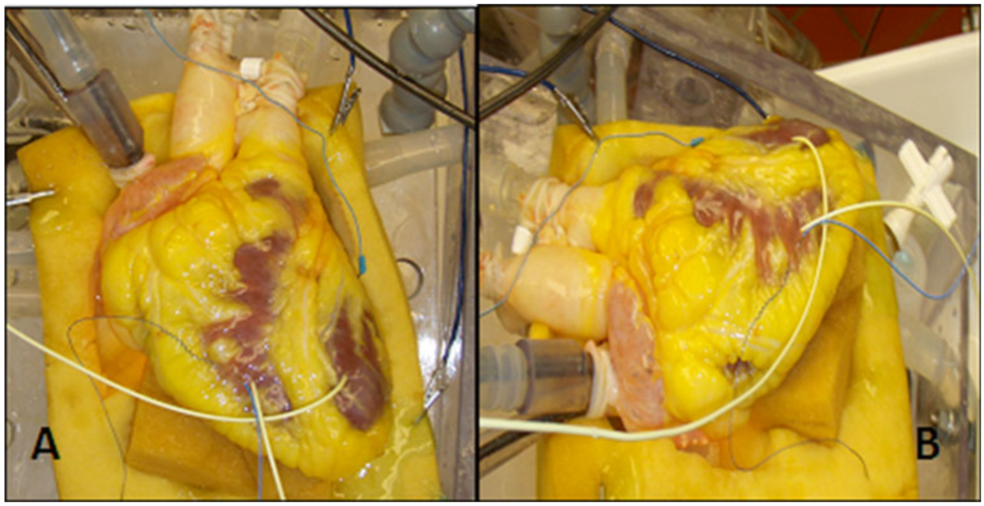

Fig. 41.3 Images of a human heart connected to the Visible Heart® apparatus from an approximation of the anterior-posterior aspect (A) and from the left anterior oblique aspect (B)

using their described PhysioHeart system [27]. However, it should be noted that in these preparations, the researchers were limited by the amount of time the heart remained viable, a factor considered key to the accessibility of the heart for device testing.

The Visible Heart® laboratory partnered with Medtronic, Inc. in 1997 to develop the Visible Heart® methodologies, which consist of a large mammalian isolated heart model that can be controlled to function in either Langendorff [25], right-side working, or four-chamber working modes [28]. Over this time and continuing today, we have been developing/optimizing this apparatus for reanimation whereby isolated large mammalian hearts are perfused and then actively pump a clear crystalloid perfusate in the place of blood. Images of a human heart connected to the Visible Heart® apparatus can be seen in Fig. 41.3. This approach has allowed our group to visualize what occurs inside the heart during device deployment procedures and subsequently to determine how such devices interact with the specific anatomies of the heart throughout all the phases of the cardiac cycle.

Briefly, our approach includes the initial step of removing hearts from humans or animals using standard cardioplegia procedures [28, 29]. Once isolated, cannulae are inserted into the great vessels allowing the placement of endoscopes or devices into all four working chambers. Following reanimation, cardiac and systemic pressures and outputs can be monitored and preloads and afterloads adjusted accordingly to simulate systemic vascular pathologies such as hypertension. Additionally, the isolated heart apparatus allows researchers to quickly switch the perfusion system to operate in Langendorff, right-side working, or four-chamber working modes. During the Langendorff mode, the left-side afterload is held constant with a coronary perfusion pressure of approximately 60 mmHg [28]; thus, the flow through the coronaries is determined by dilation or constriction of the coronary arteries. Right-side working mode combines Langendorff retrograde aortic perfusion with antegrade, or physiologic, flow through the right atrium and right ventricle (adjustable between ~3–5 L/min). During four-chamber working mode, the flow through a heart is normally determined by its intrinsic heart rate, preloads, afterloads, and the relative contractility of the various heart chambers. By controlling the orientation of the heart in our apparatus and determining the preload and afterload pressures exerted on the specimen, we can recreate specific cardiac states. Interestingly, the intrinsic heart rate and hemodynamic performance can be modified by altering the temperature of the buffer or by adding pharmacological agents (e.g., catecholamines or anesthetics), which are discussed later in this chapter. Although no model can perfectly mimic in vivo conditions, to date our apparatus has allowed researchers to simulate a broad range of particular physiological environments that are observed in various clinical settings.

41.5 How Can an Isolated Heart Prep Augment and Complement Bench Top Testing?

The combination of a "live" functional anatomy within a controlled "bench top" experimental setting provides a unique stepping stone between in vitro device testing and in vivo implantation required for implantable medical devices. Figure 41.4 shows how the typical stages of device testing and development compare in terms of the relevance of the testing environment to the intended functional environment, the quantity of data one can reasonably expect to collect, and the cost of performing such investigations. It can easily be observed that as the relevance of a particular testing methodology increases, the relative costs will dramatically

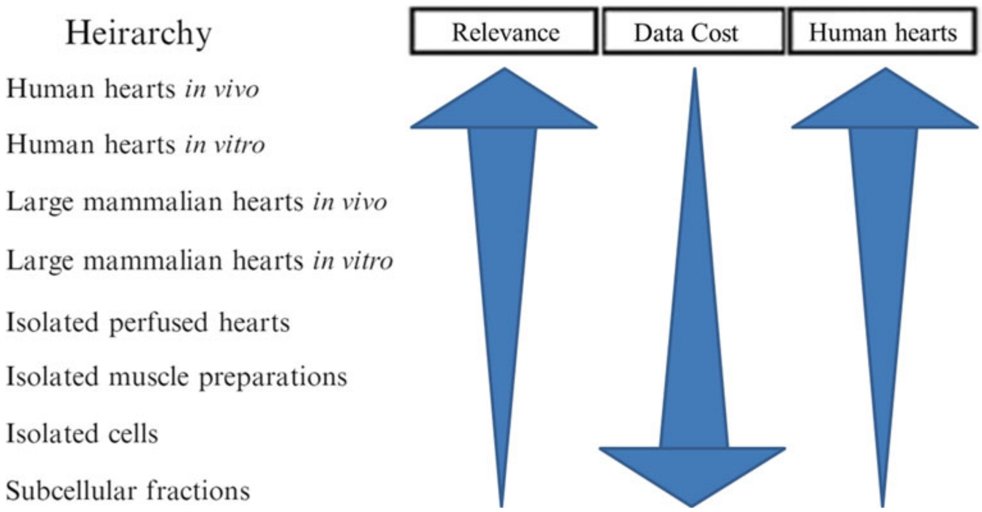

Fig. 41.4 Proposed hierarchy between the relevance of various experimental approaches, the amount of data one can obtain, and the relative costs. For example, if you wish to perform medical device design research in the field of prosthetic valves, ideally you would like to perform human trials in vivo, but this not only raises medical ethical issues but is highly costly and may provide useful data for one specific valve design and procedure. Whereas if you move the research approach downward (i.e., employ an isolated large mammalian heart model in vitro), you can obtain more data at a lower cost, but then you must justify the appropriateness of the chosen model. Yet, in one given study, it may be possible to perform multiple procedures for comparison or at least multiple implants in multiple hearts with fairly consistent anatomies

increase; thus, the likely number of possible iterations decreases. Consequently, any possible augmentations to device testing prior to chronic animal implants (e.g., via isolated beating heart preps) can, in turn, greatly reduce the overall product development costs and speed clinical use of novel valve repair, implant, and their associated delivery systems.

Due to the large number of cycles seen in the lifetime of a cardiac device, accelerated wear and fatigue testing are required gold standards for the assessment of durability. In accelerated wear testing for bioprosthetic valves, the hydrodynamic conditions are tightly controlled and easily varied allowing the durability of the valve leaflets to be assessed under a variety of predetermined conditions. Similarly, the boundary conditions imposed on the valve frame or commissure posts during fatigue testing can assess frame durability. Isolated heart preparations, including the Visible Heart® methodologies, will never replace these forms of testing, but unique information regarding the device-tissue interactions in the later can be observed. It should be noted that since the hydrodynamics of isolated heart preparations are typically less aggressive environments than what is experienced during accelerated wear testing, the boundary conditions observed for a device in such studies are not directly transferable to accelerated wear test methodologies. Yet on the other hand, they can serve as means to obtain additional information to ascertain the validity of any boundary conditions within the accelerated testing protocol, ensuring that all forms of boundary conditions have been taken into account, i.e., the change in curvature throughout the cardiac cycle of a left-sided pacing lead within the coronary vasculature. Most importantly, such experimentation has provided us with a so-called physiological link between bench top testing of devices and animal testing. Acute phenomena observed during accelerated wear testing and the insights gained with both invasive and noninvasive imaging techniques in animal studies may be directly observed during a device implant study in vitro. For example, a procedural issue observed under fluoroscopy during an in vivo animal implant could be recreated by employing the Visible Heart® approach (under direct visualization) with simultaneous fluoroscopy, thus gaining a better understanding of potential adverse issues. We consider that having the Visible Heart® apparatus as a tool for device design has allowed us to obtain a more rapid understanding of phenomena observed in both bench top and preclinical settings; as such, it is an invaluable tool for a device designer, especially at the early stages of development. See other chapters for addition descriptions and images of cardiac devices that have been implanted in reanimated human hearts [30].

41.6 The Importance of Species Selection in In Vitro Cardiac Device Research

The ultimate utility of studies performed with Visible Heart® methodologies, such as transcatheter valve development, is in part determined by the heart chosen for reanimation.

We suggest that the criteria for species selection for acute in vitro studies are slightly different from those for chronic valve assessments, due to the elimination of all systemic factors that may contribute to device performance. In other words, the species of the donor can be chosen specifically for its relative cardiac anatomy rather than for factors such as thrombogenesis, immune response, and/or growth rates.

For years, the canine heart has been used for such experimentation and has provided useful information. Yet it should be recognized that canine hearts have an unusually large amount of collateral coronary circulation (similar to humans in end-stage chronic heart failure), and this in turn results in the inconsistent creation of ischemic (infarct) regions. Sheep have been historically employed for chronic valve implantation studies, as valve function and valve orifice sizes observed in sheep are very similar to those of a human heart. Additionally, the relatively large atria of the sheep's heart allow for straightforward surgical approaches to the atrioventricular valves. However, it has recently been proposed that swine are an excellent model for acute cardiac device testing, as porcine hearts have very similar anatomy to that of humans with respect to the cardiac valves, conduction system, coronary arteries, and great vessels. Importantly the relationship between the cardiac conduction system and surrounding anatomical features is comparable between swine and human anatomies. Nevertheless, it is important to note that there are some specific variations in animal anatomy that should be known; such interindividual and interspecies variations have been extensively researched [28, 29, 31] and are described in greater detail in Chaps. 6 and 27.

Due to their specific anatomical similarity with human hearts and the relative ease of procurement (excision and reanimation), the mainstay of cardiac research done in the Visible Heart® laboratory is completed using swine hearts. Nevertheless, as previously mentioned, our laboratory has also had the privilege to obtain fresh human heart specimens for reanimation, for both educational and research purposes. Such hearts, if received in a timely manner and with complete anatomies including the great vessels, have been reanimated using the same methodologies as previously described for swine hearts. By reanimating these hearts using a clear perfusate, visualization of the internal cardiac anatomy has provided novel insights into the relative variations of human cardiac anatomy (in healthy individuals) and has highlighted the alterations that occur with various pathologies. Finally, this approach provides the unique opportunity to deliver existing or novel devices within functional human anatomies without the concerns and considerations required in clinical trials; thus, it has allowed researchers to garner invaluable knowledge about their device designs that otherwise could not be generated using animal models.

41.7 Understanding and Controlling Heart Function In Vitro

The performance of the reanimated heart can be influenced by several additional mechanisms. For example, subsequent cardiac function will be compromised by the amount of cell injury that occurs, governed in part by the amount of time between heart explant and reanimation. It is considered that if this period exceeds 6 h, performance will be compromised, even if the heart is stored under ideal conditions. To reduce such time-associated myocardial injury due to global ischemia, we have investigated the use of cardioprotective agents delivered before explanting the heart [32]. Most recently, we have been investigating the effect of omega-3 polyunsaturated fatty acids administered before explant on the acute function upon reanimation; for additional discussion of these topics, see Chap. 16.

Because of the isolation process, the reanimated heart has no direct parasympathetic or sympathetic innervation and thus is not affected by any signals from the autonomic nervous system. However, pharmaceuticals/hormones such as dobutamine and epinephrine can be administered to the circulating perfusate. These catecholamines work by stimulating the β1 receptor on the myocytes, acting as chronotropes and inotropes, increasing heart rate and contractility and, thus, overall cardiac output. Furthermore, the ionic balance of the circulating buffer can have very dramatic effects; e.g., increasing the calcium Ca^{2+} concentration in the buffer will act as a potent inotrope by increasing the Ca^{2+} inside the cell during the action potential. We will often utilize such inotropic agents shortly after deploying a prosthetic valve within an isolated heart to increase cardiac output and ejection fraction and therefore optimize function of the device.

Understanding the electrophysiology of the reanimated specimen is important during the assessment of cardiac devices and therapies designed to monitor and/or treat cardiac rhythm disease. It should be noted that by utilizing our Visible Heart® methodologies, the reanimated heart tissue is alive on the apparatus, and the heart rate is driven by the sinoatrial node. However, occasionally the heart will display an anomalous intrinsic rhythm, such as 2 to 1 block, and will consequently require pacing to ensure a consistent heart rate. This is of less concern when testing the ability of cardiac rhythm devices such as pacemakers or defibrillators to pace, as these will override any native signal to control the heart rate. However, such heart rate irregularities must be monitored and understood when testing the sensing capabilities of a particular device. For such studies, the electrophysiology can be monitored either on a gross scale using a 3-lead electrocardiogram or in detail using intracardiac electrical mapping techniques such as noncontact mapping systems. These systems are described at length in Chap. 32, and the clinical setup can be adapted to record an accurate endocardial activation map of the heart in reanimated hearts on the Visible Heart® apparatus. Such detailed assessment of the cardiac electrophysiology is of particular interest when researching cardiac ablation therapies, as electrical mapping can provide information about the size and efficacy of ablation sites. Additionally, the use of the noncontact mapping system in the Visible Heart® apparatus has augmented the assessment of acute post-procedural conduction complications during transcatheter aortic valve implantations. See also Chaps. 29 and 36 for additional discussion of these devices.

41.8 Comparative Imaging in the Visible Heart® Apparatus

The ability to reanimate, control, and optically visualize human hearts has allowed for the collection of unique videoscopic footage of the functional human heart [28, 29]. By utilizing endoscopic video systems in conjunction with clinically relevant imaging modalities, such as fluoroscopy (continuous X-ray) and cardiac ultrasound (echocardiography), we have been able to create novel comparative anatomy footage. This has provided a direct visualization of what the physician would see in the clinical setting and has also offered valuable insights into device and delivery system performance. Examples of the imaging capabilities of the Visible Heart® methodology within a human specimen can be seen in Fig. 41.5. In addition to video images of the functional anatomies, extensive footage of device implantations has been obtained utilizing Visible Heart® methodologies, including transcatheter-delivered valve prostheses to the pulmonary and aortic positions as seen in Figs. 41.6 and 41.7 [33, 34]. Such visualization of the delivery of a transcatheter pulmonic valve has provided new information to assist designers in the adaptation of the valve leaflets in the pulmonary position to accommodate the low pressure gradients that may be encountered in this anatomic location [33]. Furthermore, the implantation of transcatheter aortic valve replacements into the native aortic root of human hearts has highlighted the interaction of the frame with the native leaflets of the mitral valve and the interventricular septum, thus illustrating the importance of precise frame sizing and positioning in order to avoid interaction with the anterior leaflet of the mitral valve and excessive pressure on the cardiac conduction system [34]. Such simultaneous imaging in the Visible Heart® can be used

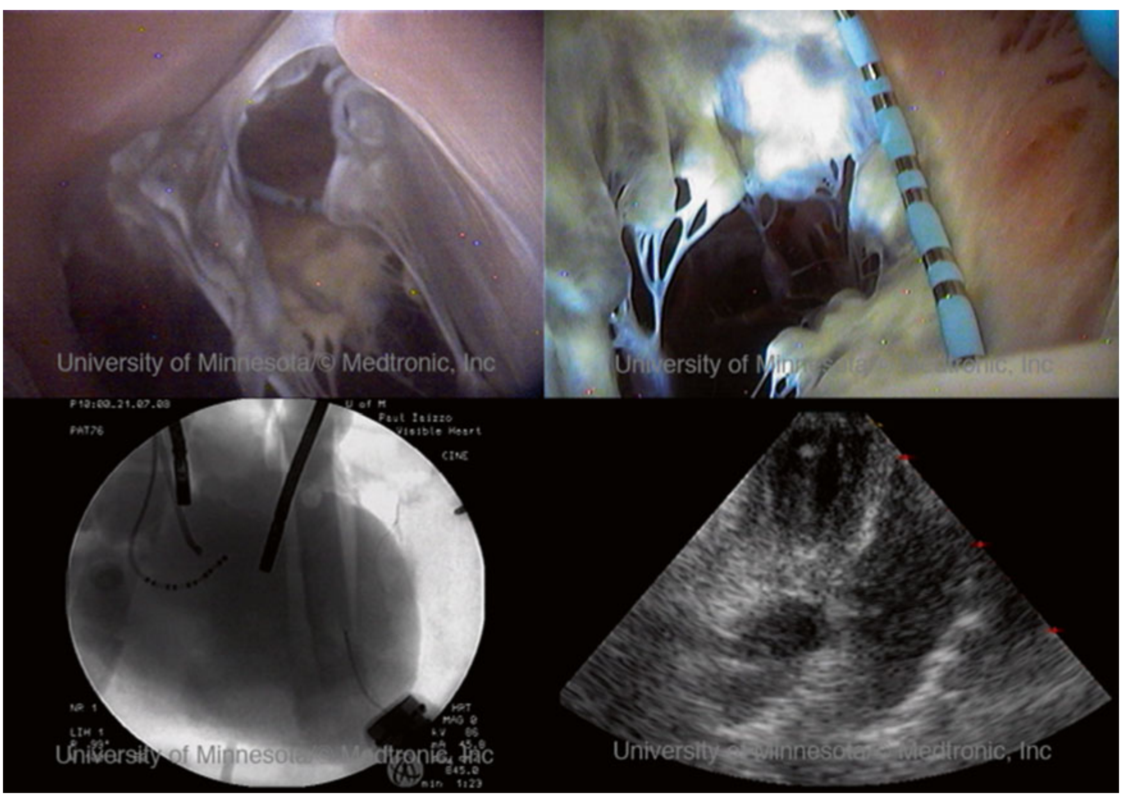

Fig. 41.5 Unique views of the tricuspid valve within a reanimated human heart imaged using (1) an endoscope placed within the right ventricle (*upper left panel*), (2) an endoscope placed within the right atrium (*upper right panel*), (3) fluoroscopy with an anterior-posterior orientation (*lower left panel*), and (4) ultrasound (*lower right panel*). Modified from The Atlas of Human Cardiac Anatomy [29]

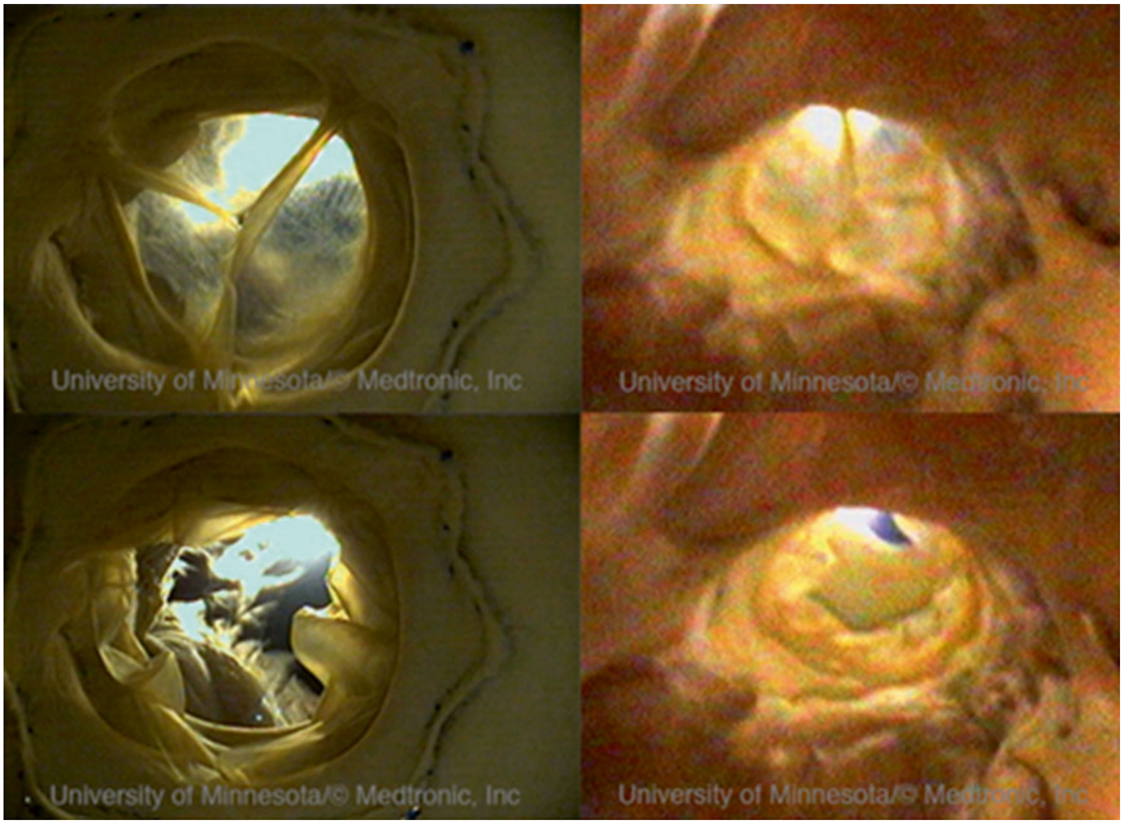

Fig. 41.6 Images of a transcatheter-delivered pulmonary valve which was imaged with endoscopes placed within (1) the pulmonary trunk during diastole (*upper left panel*), (2) the right ventricle during diastole (*upper right panel*), (3) the pulmonary trunk during systole (*lower left panel*), and (4) the right ventricle during systole (*lower right panel*). Modified from Quill et al. [33]

to capture unique internal and/or external images of device implantations during near normal hemodynamic conditions (left ventricular systolic pressures of 70–90 mmHg).

41.9 The Portable Visible Heart®

Due to the inherent advantages of MRI and CT for assessment of cardiac function and anatomy in vivo, it was considered desirable for our group to develop a portable Visible Heart® system which would allow MR or CT imaging of an isolated beating heart. A portable system would enable physiologic perfusion of an isolated large mammalian heart during simultaneous MR or CT imaging. Full details of the development of a portable apparatus and associated methodologies for isolated heart imaging in the CT and MRI environment were described by Eggen et al. [35]. Briefly, one needs to first consider the strong magnetic field in the MR environment that poses specific design challenges; we considered that this required the construction of a two-unit system to remove all ferromagnetic materials from the proximity of the MR scanner. The apparatus contains the necessary preload and afterload chambers required for physiological cardiac function (i.e., Langendorff or four-chamber working modes) and allows for independent control of the chambers in order to augment the pressure gradients across the valves. This novel system allows for the isolated heart to be placed safely on the patient bed of the scanner (Fig. 41.8).

To date, this system has been successfully used to obtain MR and CT images in both swine and human hearts (Figs. 41.9 and 41.10) [35, 36]. We consider that some of the advantages of isolating and reanimating a heart within the MRI/CT environment for device testing with such a portable system include the following:

- High-resolution studies of use conditions or device-tissue interactions with precise controls over physiological conditions. Without the need for breath holds, as is required for the intact animal or human scan sessions, image averaging and sequence times can be increased, thereby increasing the ultimate signal-to-noise ratios.
- The function and efficacy of MRI-safe devices can be tested in a dynamic beating heart environment without the costs incurred during intact animal testing.
- Comparative imaging. Direct imaging methods (i.e., endoscope) can be subsequently compared to MRI/CT imaging

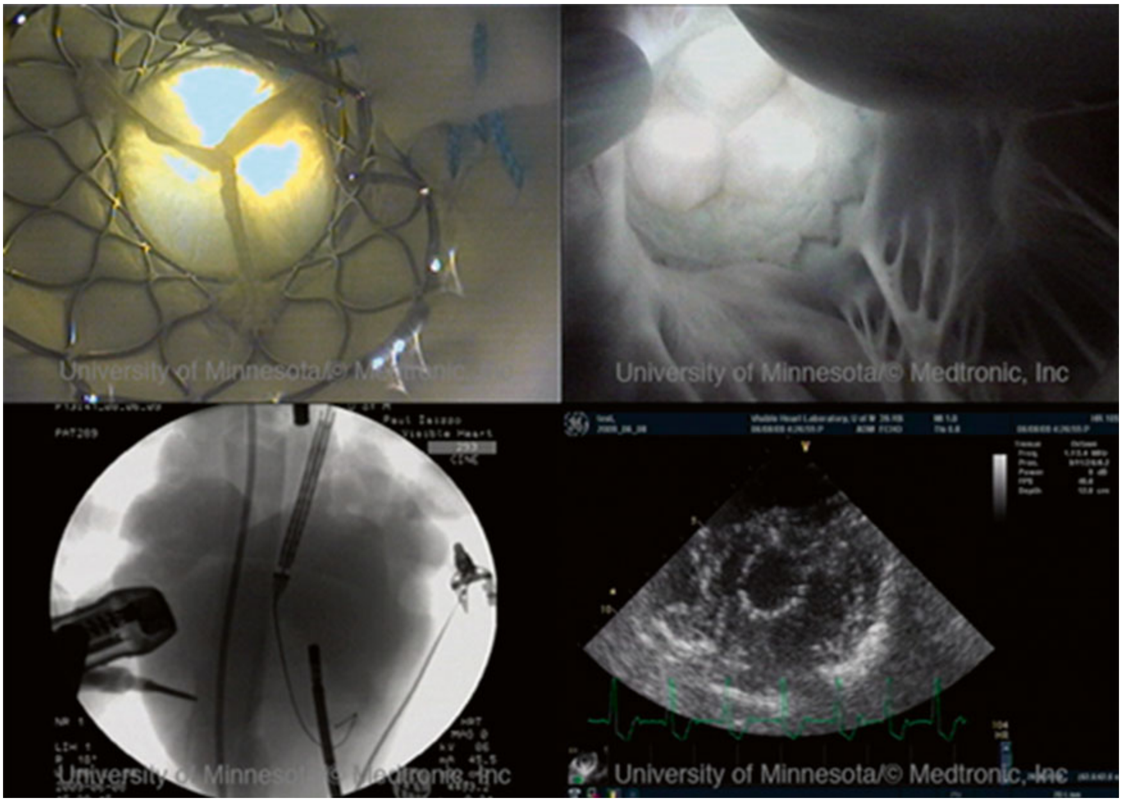

Fig. 41.7 Images of a transcatheter-delivered aortic valve imaged using (1) an endoscope placed within the ascending aorta (*upper left panel*), (2) an endoscope placed within the left ventricle (*upper right panel*), (3) fluoroscopy with an anterior-posterior orientation (*lower left panel*), and (4) ultrasound (*lower right panel*). Modified from Iaizzo et al. [34]

of cardiac function and anatomy or interaction with devices as a means to evaluate the best clinical imaging modalities for the desired target variable/interaction of interest.

- Multiple device implantation studies can be conducted under endoscopic visualization before analyzing the implantations using MRI/CT imaging, without requiring an XRM suite or combination CT-X-ray surgical suite.

41.10 Limitations of Visible Heart® Methodologies

The Visible Heart® methodologies are not without known limitations. For example, ischemic time prior to reanimation can compromise cardiac function, specifically contractility and thus pressure generation. Additionally, the lack of a pericardium may contribute to overexpansion of the atrial chambers, slightly different respective anatomical orientations of the great vessels and chambers, and/or differences in contractility compared to in vivo performance. However, it should also be noted that one can isolate these large mammalian hearts for the use with the pericardium primarily intact [37]. Additionally, the relative positioning of a given heart on the apparatus may also affect its overall performance. Furthermore, the use of a clear perfusate, without a specific oxygen carrier (i.e., a hemoglobin substitute like a perfluorocarbon), will lead to progressive global ischemia and the development of tissue edema which has effects on the long-term viability of these reanimated hearts.

The altered hydrodynamic state of the heart and progressive edema that occurs during reanimation on the Visible Heart® apparatus limits use of the apparatus for certain types of device testing. For example, deterioration of the tissue does not allow for chronic valve testing and limits most investigations related to the acute consequences of device implantations. Additionally, bench top tests such as accelerated wear testing have established guidelines for testing valves, which cannot be reliably reproduced on the Visible Heart® apparatus. Valve testing conducted in animals typically includes an artificially induced "challenge" state, which produces hemodynamic profiles that are unattainable on the isolated heart preparation. In other words, while the Visible Heart® apparatus in its current form does not replicate or replace bench top or preclinical testing, it can provide unique comparative imaging of functional anatomy and device-tissue interface which is not available in bench top or preclinical animal testing.

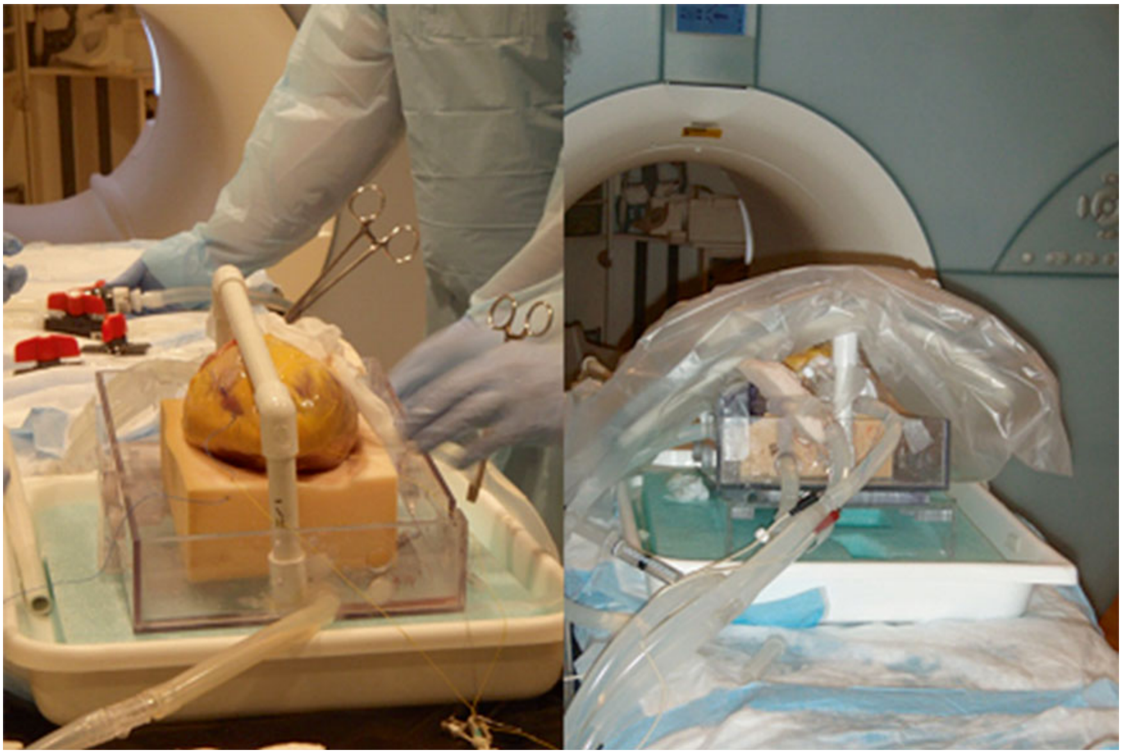

Fig. 41.8 Portable Visible Heart® apparatus. The isolated heart support system enables the heart to be positioned in the anatomically correct position during imaging in a magnetic resonance scanner (*left panel*; human heart shown). The isolated heart system with receiver coil positioned on the patient bed prior to MR imaging (*right panel*)

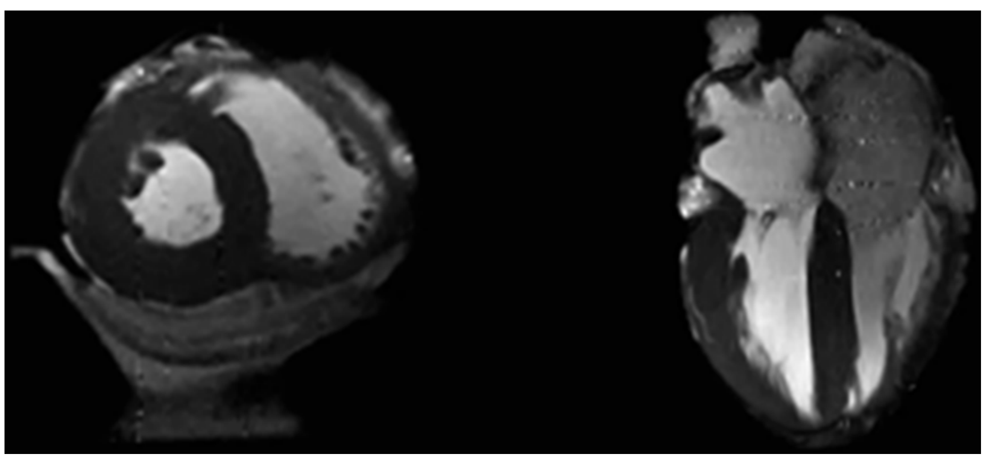

Fig. 41.9 MRI images obtained from a reanimated human heart placed in a 1.5 T MRI scanner: short-axis view (*left*) and long-axis view (*right*)

41.11 Acute Testing of Pathological Animal Models

The successful reanimation of human hearts using the Visible Heart® approach described in this chapter requires a level of cardiac health not always present in the available specimens (those deemed nonviable for transplant). Additionally, it is considered that the therapies for a specific category of pathologies often cannot be adequately or ideally tested by using "healthy" swine hearts as a model (e.g., severe aortic stenosis, dilated cardiac myopathy, or complex cardiac arrhythmias). In order to test therapies for these pathologies, a number of acute animal models have been created to mimic the anatomy and morphology of various human disease states. One example of this has been the development of various models for severe aortic stenosis, e.g., with the specific aim of determining how large calcific deposits on the leaflets affect the deployment and function of devices. To approximate severe stenosis of the aortic valve, we have: (1) directly

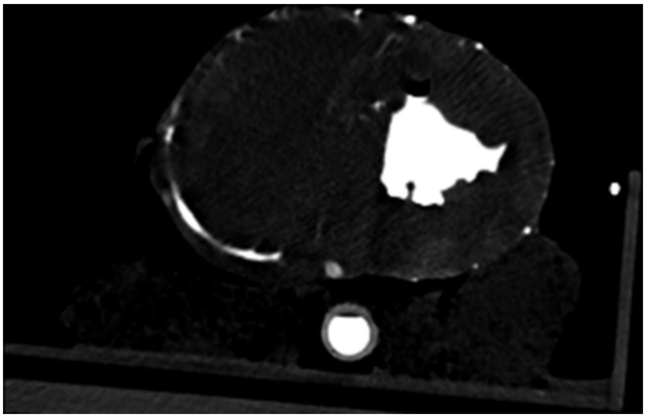

Fig. 41.10 Contrast-enhanced CT image of an isolated swine heart. The right coronary artery, aorta, and left ventricular endocardium are enhanced

adhered plastic models of calcification to the leaflets to reduce leaflet motion and (2) partially adhered the leaflet commissures to reduce the effective orifice areas of these valves. To date, such a model has allowed for expanded procedural testing of these devices (e.g., from balloon valvuloplasty to device deployment), providing useful insights into device performance as well as the potential interaction of deployed devices and the calcific deposits relative to the native anatomy. Another example has been the chronic use of high rate pacing to force the heart to remodel and dilate, mimicking the shape and function of patients with end-stage heart failure that often require cardiac resynchronization therapy. The ability to deliver, implant, and ensure capture of left-sided pacing leads in the relevant cardiac vascular anatomy has allowed designers to fine-tune lead and delivery system performance before entering into preclinical or first in man testing.

With the understanding that testing cardiac devices in relevant anatomies is key for better prediction of in vivo performance, there is ongoing research to further develop models, specifically models designed to simulate certain pathological states to test devices and delivery systems.

41.12 Future Directions

As anatomical resources develop and functional in vitro cardiac systems such as the Visible Heart® library and methodologies continue to evolve, so will the research possibilities within the realm of anatomical visualization and in vitro reanimation. Further, successful collaborations with the University of Manchester (UK) and Washington University (St. Louis, MO, USA) have been cultivated to determine the particular anatomical structure of the cardiac conduction system [38, 39]. Additionally, continued imaging should provide further anatomical information on cardiac disease states highlighting how disease management could, in turn, be effecting reverse remodeling on a cellular scale as well as a global scale of cardiac anatomy. Currently, all collected datasets (videoscopic, CT, echocardiographic, and MRI) are being used to create a digital database of human anatomies by rendering 3D computational models using software packages such as Mimics (Materialise, Leuven, Belgium); such datasets are being used to create physical representations of certain specimens via 3D printing [12]. Along with the plastination of select specimens, our work in creating real-life and computational 3D models (e.g., for both object printing and computation simulations) will pave the way for ongoing investigations and provide anatomically correct models for investigations related to device design and/or for educational purposes.

In addition, our laboratory is continually improving the Visible Heart® methodologies with systems designed to optimize the physiological function and control of the heart to improve the reproducibility, longevity, and utility of investigations. New cardioplegia and perfusate solutions are being tested as means to better protect the heart from ischemia and edema (some may be delivered as a pretreatment to specimens before extraction). Further, there is a continuing need to modify the setup/apparatus itself to better accommodate various delivery system designs (such as subclavian and femoral access systems). It should also be noted that the use of Visible Heart® methodologies to augment chronic studies has allowed for the validation of surgically created anatomies and the direct visualization of chronic device implants that were not previously possible. We consider that the utilization of both fixed specimens and Visible Heart® methodologies for device evaluation should be used in a complementary fashion with other techniques that utilize in vivo or in vitro methods to test the reliability, durability, biocompatibility, and/or other design parameters of newly developed transcatheter-delivered devices [30]. There is little doubt that the continued testing of novel cardiac prostheses via in vitro and in vivo studies will provide scientists, engineers, and/or clinicians working in this field with the necessary tools to drive the required research and development of the next generation of transcatheter-delivered cardiac devices.

41.13 The Atlas of Human Cardiac Anatomy

As novel therapies become clinically available and are implanted by more and more physicians, individuals will require continued education in the techniques required to navigate and deploy such devices. In response to this need, our laboratory has created a free access website, The Atlas of Human Cardiac Anatomy (www.vhlab.umn.edu/atlas), which can be utilized by cardiac device developers and clinical implanters to gain insights on the relative variability in functional cardiac anatomy [12]. This website uniquely includes downloadable movie clips of functional cardiac anatomy; comparative imaging using echo, fluoroscopy, and MRI; and digital reconstruction images obtained from the human hearts of organ donors whose hearts were deemed not viable for transplant.

41.14 Summary

In summary, the study of fixed and reanimated human hearts, using the various methodologies described here, provides an individual with novel insights on normal and pathological human cardiac anatomies. Additionally, one can better visualize anatomical alterations that occur with specified pathologies and/or those that may occur following the deployment of devices within the heart. More specifically, the Visible Heart® methodologies to reanimate large mammalian hearts have provided a unique perspective on functional cardiac anatomies. By reanimating hearts using a clear perfusate, we are able to visualize functional anatomies with endoscopes placed directly within various heart chambers and/or within the vessels of the heart. Such anatomical knowledge is critical for device designers and developers, as well as clinicians who utilize these less invasive cardiac repair approaches for patients with acquired or congenital structural heart defects. Furthermore, when direct visualization is simultaneously coupled with clinically employed imaging modalities, it provides critical insights that can be used to more quickly and precisely advance such technologies. We consider that the utilization of both fixed specimens and Visible Heart® methodologies for device evaluation should be used in a complementary fashion with other techniques that utilize in vivo or in vitro methods to test the reliability, durability, biocompatibility, and/or other parameters of newly developed transcatheter devices. The continued testing of novel cardiac devices via in vitro and in vivo studies will provide scientists and engineers working in this field with tools to drive the required research and development of the next generation of cardiac devices.

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