Symposium Article

New frontiers in the pathology and therapy of heart valve disease: 2006 Society for Cardiovascular Pathology, Distinguished Achievement Award Lecture, United States–Canadian Academy of Pathology, Atlanta, GA, February 12, 2006

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Abstract

This review summarizes several areas relative to the pathology of heart valve disease in which there has been rapid and ongoing evolution, namely, our understanding of: (a) the dynamic functional biology of cardiac valves; and (b) the pathology/pathobiology of valvular heart diseases; (c) new developments in valve repair and substitution using percutaneous approaches; and (d) progress toward the exciting potential of therapeutic valvular tissue engineering and regeneration, including the challenges that will need to be overcome before such therapeutic advances can become clinically useful. © 2006 Elsevier Inc. All rights reserved.

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1. Introduction

This review summarizes several areas in the broad field of the pathology of heart valve diseases in which there has recently been either important new data, conceptual advances, or technological evolution, including: (a) the dynamic functional biology of cardiac valves; (b) the pathobiology of valvular heart diseases; (c) new developments in valve repair and substitution, particularly progress in using percutaneous approaches; and (d) progress toward the exciting potential of therapeutic valvular tissue engineering and regeneration, including the challenges that will need to be overcome before this type of therapy can be translated to the clinical arena. This communication supplements and extends a brief review in this general area published by the author in Cardiovascular Pathology approximately 1 year ago [1].

2. Dynamics of valvular structure, function, and biology

Key physiologic structure–function correlations of the native aortic valve are well known [2]. Appreciation of these essential relationships facilitates an understanding of valve pathology and the mechanisms of valvular diseases, fosters the development of improved tissue heart valve substitutes, and facilitates innovative approaches to heart valve repair and regeneration [3–5]. We review several studies that have fostered an emerging picture of how valves form embryologically, mature in the fetus, and adapt, maintain homeostasis, and change throughout life.

During the normal development of the heart, the heart tube undergoes looping, following which valve cusps/leaflets originate from mesenchymal outgrowths known as endocardial cushions [6–9]. A subset of endothelial cells in the cushion-forming area, driven by signals from the...
endothelial cells express different markers [12], and aortic
thelial cell heterogeneity). For example, venous and arterial
differences in gene expression and other properties (endo-
lated from different vascular and valvular sources display
272
stimulation in vitro and in vivo [20–24]. When stimulated by
adaptation when valves or cells are exposed to environmental
[18,19], modulate their phenotype, and mediate functional
from the tissue environment and placed in in vitro culture
interstitial cells are predominantly fibroblast-like in intact
ation, and reorganization of its ECM, which depends on
physiologic remodeling that entails the synthesis, degrada-
mention of valvular ECM is the overwhelming determinant of valve
produced and maintained by VIC, and the quality of the
muscle cells, and myofibroblasts. The valvular ECM is
possess a dynamic structure composed of proliferating cells,
a nascent ECM, and α-SMA-positive cells, which are indicative of myofibroblasts [27]. Pulmonary and aortic
fetal VIC show an activated myofibroblast-like phenotype
(α-actin expression), abundant embryonic myosin, and
MMP collagenases, indicating an immature/activated phe-
otype engaged in matrix remodeling versus a quiescent
fibroblast-like phenotype in adults; VIC density, prolifera-
tion, and apoptosis are markedly higher in fetal valves than
in adult valves, perhaps reflecting a progressive adaptation to
hemodynamic conditions. Moreover, the VEC of fetal valves
are positive for Smemb, an embryonic form of myosin heavy
chain, MMP-1 and MMP-13, and other markers of endo-
thelial-activated phenotypes such as ICAM-1 and VCAM-1.
Collagen fiber alignment also occurs progressively during
the maturation of valve leaflets. Hence, dynamic changes
in cell phenotype, cell proliferation, apoptosis, and ECM
remodeling occur after endocardial cushions have evolved
into leaflets and continue throughout human fetal develop-
ment, postnatal development, and life. Indeed, valvular homeostasis seems to be an active process, and there is
good evidence that its dysregulation can lead to pathology, as
emphasized later. Moreover, ongoing changes in valve
structure related to both cells and ECM lead to changes in
mechanical properties and potential function, as evidenced by
increasing valve stiffness with increasing age [28].

3. Pathobiology of valvular heart disease

There is increasing evidence that the pathogenesis of
nonrheumatic aortic and mitral valve diseases may have a
more prominent genetic component than previously recog-
nized [29]. For example, genetic determinants of atheroscle-
rosis may contribute to aortic stenosis [30]; bicuspid aortic
valve (BAV) and other congenital deformities of the ventric-
ular outflow tracts may be heritable in many cases [31]; and
mitral valve prolapse (MVP) may be related to aberrations of
key remodeling events that are both involved in physiological
valve homeostasis and genetically determined [32]. We
describe some recent data that support these contentions.

3.1. Evolving insights on degenerative and heritable factors
in aortic valve disease

With a prevalence of approximately 1%, BAV is the most
frequent congenital cardiovascular malformation in humans
Although BAV is usually uncomplicated early in life, complications of BAV, including aortic stenosis or regurgitation, infective endocarditis, and aortic dilation and/or dissection, are important later in life. BAV underlies over two thirds of aortic stenosis in children and 50% of aortic stenosis in adults [34]. Aortic abnormalities commonly accompany BAV, even when the valve is hemodynamically normal [33].

Recent studies have confirmed previous reports of familial clustering of BAV and left ventricular outflow tract obstruction malformations, and their association with other cardiovascular malformations [35,36]. A high genetic determination suggests that these common valvular malformations are primary to defective valvulogenesis or are secondary to other elements of cardiogenesis. Particularly interesting in this regard is the recent report that mutations in the signaling and transcriptional regulator NOTCH1 cause a spectrum of developmental aortic valve abnormalities and severe calcification in two families with non-syndromic familial aortic valve disease [37].

Acquired aortic stenosis is usually the consequence of calcification intrinsic to the cuspal tissue, owing to progressive and advanced-age-associated “wear and tear” of either previously anatomically normal aortic valves or BAV [38]. With the rising average age of the population, the prevalence of aortic stenosis, estimated at 2%, is increasing [39]. The mechanisms of aortic valve calcification are traditionally believed to be due to degenerative, dystrophic, and passive accumulation of hydroxypatite minerals in the setting of sclerosis [40]. Although it is likely that calcification is promoted by decreasing VIC number and matrix stiffening that occur progressively throughout life (as described above) and that mechanical damage to VIC plays an important role in degenerative aortic valve stenosis, the mechanisms have not yet been explored. Moreover, recent studies suggest active regulation of calcification in aortic valves similar to that in atherosclerotic arteries, with inflammation, lipid infiltration, and phenotypic modulation of VIC to an osteoblastic phenotype [41–43]. This has stimulated interest in the possibility that statin drugs may decrease the rate of aortic stenosis progression, but studies to date have not supported this contention [44,45].

3.2. Progress in understanding the significance and pathophysiology of myxomatous degeneration of the mitral valve

Mitrval valve prolapse (MVP), the clinical expression of myxomatous degeneration of the mitral valve, is the displacement of enlarged, thickened, redundant mitral leaflet(s) into the left atrium during systole [46]. Histologically, the essential change is attenuation of the collagen-rich fibrosa layer of the valve, on which the structural integrity of the leaflet depends, accompanied by focally marked thickening of the spongiosa layer with deposition of myxomatous material rich in proteoglycans. Over the last decade, owing to improved technology and large community studies, a 2.4% prevalence of MVP and a ≤3% rate of serious complications, namely, heart failure, mitral regurgitation, bacterial endocarditis, thromboembolism, and atrial fibrillation, have been ascertained [47]. MVP is presently the most common indication for surgical repair or replacement of the mitral valve.

It is well accepted that MVP has, at least in some cases, a hereditary component. MVP is associated with some heritable disorders of connective tissues, including Marfan syndrome, in which it is usually associated with mutations in Fibrillin-1 (FBN-1) [48]. However, most cases of MVP are unassociated with FBN-1 abnormalities; indeed, it is unlikely that more than 1–2% of patients with MVP have an associated connective tissue disorder [49].

MVP in both genetic and acquired disorders is associated with the weakening of valvular connective tissues. The prevailing concept is that there is a deficiency in the mechanical integrity of leaflets, possibly owing to a genetic defect. Together with normal wear and tear, this leads to stretching and elongation, thereby giving rise to the clinical phenotype of MVP, including thickening and microscopic destruction of fibrillar connective tissues. The problem could be located in essential structural proteins and proteoglycans, or in processes of valvular ECM remodeling, which could involve cells or their products such as MMPs or other key mechanisms in ECM production or degradation. Indeed, we have demonstrated that VIC in this disorder are activated, suggesting a state of chronic mechanical disequilibrium [50]. A recently developed mouse model of MVP implicates a role for TGF-β dysregulation in connective tissues in Marfan-syndrome-related and possibly other forms of MVP [51].

Studies utilizing genetic linkage analysis have mapped families with autosomal dominant MVP to the X-chromosome [52] and to chromosomes 11p15.4 [53] and 16p11.2–p12.1 [54]. Recently, a third chromosomal locus for MVP has been identified on chromosome 13q31.3–q32.1 [55]. This locus is particularly interesting in that there are at least 16 known genes in the region, several of which could be involved in valvular remodeling and appear to be good candidates for MVP.

3.3. Ischemic mitral regurgitation (IMR): renewed interest in an old lesion

There has been renewed interest in IMR, also called functional mitral regurgitation; in IMR, the leaflets are intrinsically normal, while ventricular structure and function are altered by ischemia [56,57]. IMR is present in 10–20% of patients with coronary artery disease and worsens prognosis following myocardial infarction, with reduced survival directly related to the severity of the regurgitation. Papillary muscle dysfunction alone is insufficient to produce IMR; key causal factors are dilation and the increasing spherical shape of the left ventricle, which pulls the papillary muscles down and away from the center of the chamber. Although there is substantial interest in developing
surgical and/or percutaneous approaches to the repair of IMR, none of the strategies developed so far has resulted in clearly improved patient outcomes [58].

4. Heart valve substitution and repair

Replacement of diseased cardiac valves by prostheses is common and often life-saving [59], yet approximately 60% of substitute-valve recipients [with either mechanical, prosthetic, or bioprosthetic valves (fabricated from porcine aortic valve or bovine pericardium)] develop a serious prosthesis-related complication within 10 years postoperatively [60]. Thromboembolic complications comprise the major problem with mechanical valves, necessitating long-term anticoagulation in patients with these devices; this therapy reduces thromboembolism but can induce hemorrhagic complications [61]. Structural deterioration uncommonly causes failure of contemporary mechanical valves but is the major failure mode of bioprostheses, usually with calcification and/or tearing, causing secondary regurgitation [62].

Cuspal mineralization and noncalcific structural damage are the major mechanisms of tissue failure that cause structural deterioration [62,63]. Tissue valve calcification is initiated primarily within the residual porcine VIC that have been devitalized, usually by glutaraldehyde pretreatment. The mechanism of calcification involves the reaction of calcium-containing extracellular fluid with membrane-associated phosphorus to yield calcium phosphate mineral deposits. Calcification is accelerated by young recipient age, valve factors such as glutaraldehyde fixation, and increased mechanical stress. Recent studies have suggested that pathological calcification is regulated by inductive and inhibitory factors, similar to the physiologic mineralization of bone [64]. New prostheses pretreated with anti-calcification agents (that remove or alter the cellular phospholipid substrate) are being used in several commercial valves, but the extent of improvement in long-term durability is not yet known. However, it appears that damage to the valvular collagenous skeleton will likely become the ultimate limiting factor in durability in valves protected from calcification [65].

4.1. Percutaneous valve replacement and repair

Many patients with certain types of valvular heart disease now have surgical valve repair instead of replacement, and recent reports suggest that endovascular procedures may provide an alternative to open heart operations. New catheter techniques for inserting stent-mounted prosthetic valves within stenotic aortic and pulmonary valves, and for emulating surgical repair of regurgitant mitral valves, are in various stages of preclinical development and clinical testing [66–68]. Percutaneous implantation of a foldable heart valve that can be mounted on an expandable stent, delivered percutaneously through standard catheter-based techniques, and implanted within a diseased valve annulus may be possible. Other endovascular approaches include percutaneous placement of a mitral annular constraint device in the coronary sinus and double-orifice edge-to-edge mitral valve repair [69] without cardiopulmonary bypass for the treatment of mitral regurgitation [70]. Percutaneous valve intervention is most likely to be used in patients with severe diseases deemed inoperable, in patients with early-stage regurgitant lesions in whom valve repair may prevent progressive ventricular dilation, and in patients with congenital heart disease wherein percutaneous pulmonary valve replacement may find a distinct niche to obviate the morbidity of reoperation to replace malfunctioning pulmonary conduits.

4.2. Percutaneous replacement of semilunar valves

Percutaneous valve replacement uses an outer stent-like structure that contains leaflets; these two components together constitute a functioning valvular prosthesis. The stent holds open a valve annulus or a segment of a prosthetic conduit and resists the tendency of a vessel, the valve annulus, and diseased native leaflets to recoil following balloon dilation; supports the valve leaflets; and provides the means for the seating of prosthesis in the annulus or in the vessel. In patients with repaired congenital heart disease, complications of a right-ventricle-to-pulmonary-artery conduit are frequent, and the opportunity for palliation to delay or prevent surgery is attractive in many cases. For aortic valve disease, excellent clinical success with surgical aortic valve replacement restricts the use of balloon valvuloplasty/percutaneous valve replacement in nonsurgical candidates, or as a bridge to valve replacement in patients in whom surgery needs to be delayed.

Several valve designs for endovascular implantation are under development and testing. Valves composed of either a shape-memory nitinol alloy stent (which is self-expandable) housing a valve constructed of porcine pericardial leaflets, a platinum–iridium alloy stent with a bovine jugular vein valve, or a stainless steel cage (which is balloon-expandable) with equine pericardial leaflets have had the most extensive clinical application in more than 100 patients [71,72]. This early clinical experience demonstrates both the feasibility of percutaneous valve replacement in aortic and pulmonary locations, and the potential and challenges of transcatheter valve replacement. Given the overall clinical success of this approach to date as well as the morbidity associated with reoperative surgery in repaired congenital heart disease, percutaneous pulmonary valve replacement is the most likely of all the catheter-based valve technologies to achieve near-term broad clinical application.

Key challenges are associated with the use of stent-mounted prosthetic valves. Valved stents are significantly larger than most existing percutaneous cardiac catheters and devices, and presently in the order of 22–24 F. In the aortic
position, there is the potential to impede coronary flow or to interfere with anterior mitral leaflet mobility, the conduction system, or native diseased leaflets. Stent architecture may also preclude future catheter access to the coronaries for possible interventions. Secure seating within the aortic annulus or pulmonary conduit and the long-term durability of both the stent and the valve tissues are also major considerations.

4.3. Percutaneous repair for mitral valve regurgitation

Percutaneous balloon mitral valvuloplasty has been used to treat mitral stenosis for over two decades [66], with excellent success in patients with suitable valvular and subvalvular morphology. However, there has been no clinically useful percutaneous treatment for patients with mitral regurgitation. Percutaneous approaches currently being evaluated for mitral regurgitation attempt to emulate one or more of the components of surgical mitral valve repair, including annular reduction (usually by an annuloplasty ring) and edge-to-edge repair. However, leaflet resection and chordal modification cannot be easily done via a catheter.

Percutaneous approaches in various stages of development and clinical evaluation include implantation of a device in the coronary sinus, left atrium, or both, or by device placement behind the posterolateral leaflet of the mitral valve (at least three devices employing this concept are currently on clinical trial) [67,70]. The goal is to plicate or straighten the posterior mitral annulus. A major challenge of coronary sinus approaches relates to the anatomic variability of the coronary sinus, which, in many patients, is located 1 cm or more above the mitral annulus. Additional annuloplasty approaches, presently in preclinical testing, include a suture annuloplasty from the ventricular side of the mitral annulus, thermal modification of the annulus to obtain shrinkage, and a percutaneous ventricular restraint system that attempts to reshape the left ventricle. Another approach uses an edge-to-edge clip prosthesis emulating the edge-to-edge surgical (Alfieri stitch) repair in which the midportions of the anterior and posterior mitral leaflets are sutured together, which is used as an adjunctive or even primary repair modality in some patients with predominant leaflet prolapse [69].

5. Heart valve regeneration and tissue engineering

Recent 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. This progress includes: (a) evolving insights into the mechanisms of cardiac valve development, homeostasis, adaptation, and response to injury; (b) recognition of the inadequacies of current surgical and interventional approaches to treat existing valvular heart disease; (c) substantial understanding of the mechanisms of complications in existing biological valve replacements; and (d) technological advancements in biomaterials, imaging, and minimally invasive surgical and catheter-based access to the heart and to the circulation. Innovative work toward this objective is active in many laboratories and may eventually lead to clinical application. The long-term success of a tissue-engineered (living) valve replacement will depend on the ability of its living cellular components (particularly VIC) to assume normal function, with the capacity to repair structural injury, remodel the ECM, and potentially grow [4,5,73].

Three approaches are under consideration: (a) use of the methodology of tissue engineering, i.e., combining cells with scaffold in a bioreactor environment to generate a tissue formed in vitro, which is then implanted (in vivo) to form an organ or a tissue; (b) recruitment of endogenous cells through circulation from the bone marrow or other sources; and (c) harnessing of the intrinsic regenerative potential of the heart valves. The most widely followed paradigm of tissue engineering seeds cells on a synthetic polymer or a natural material scaffold formed into the shape of the ultimate implant; a tissue generated by seeded cells is matured in vitro (in a bioreactor that provides a suitable metabolic and mechanical environment). The cells differentiate, proliferate, and produce ECM to form a living model of the ultimate organ or tissue, which is called a construct [74]. Subsequently, the construct is implanted in the desired anatomic location as a prosthesis, where further remodeling in vivo occurs to recapitulate the normal functional architecture of an organ or a tissue. Key processes occurring during the in vitro and in vivo phases of tissue formation and maturation are as follows: (a) cell proliferation, sorting, and differentiation; (b) ECM production and organization; (c) degradation of the scaffold; and (d) remodeling and potential growth of tissues.

Tissue-engineered heart valves (TEHV) grown as valved conduits from autologous cells (either vascular wall cells and bone-marrow-derived mesenchymal stem cells) seeded on biodegradable synthetic polymers grown in vitro have functioned in the pulmonary circulation of growing lambs for up to 5 months [75,76]. Particularly interesting is that the constructs produced in vitro evolved in vivo to a specialized layered structure that resembled that of native semilunar valves. These studies demonstrate that a tissue grown in vitro can function as a valve replacement in vivo and can serve as a template for the remodeling of tissues toward a structure with appropriate functional morphologic characteristics. A recent study has shown that 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 and reached a stable functional state and morphologic appearance, with viable cells in a fibrous matrix deep in the wall and an endothelial-cell-lined smooth-muscle-cell-con-
natural degradable polymeric scaffolds, such as collagen or other precursor cells [78]. Investigators have used decellularized and growth of circulating endothelial cell progenitors and attract and provide a fertile environment for the adherence and growth of circulating endothelial cell progenitors and other precursor cells [78]. Investigators have used decellularized tissue scaffolds derived from valves, the pericardium, and cell-free porcine small intestinal submucosa or natural degradable polymeric scaffolds, such as collagen or fibrin gel [79]. Natural-tissue-derived valve scaffolds possess desirable three-dimensional architecture, mechanical properties, and potential adhesion/migration sites for cell attachment and ingrowth. Nevertheless, decellularized porcine valves implanted in humans induced a strong inflammatory response and suffered from structural failure, which has inhibited further use [80]. Despite practical failure to date, the concept of a natural scaffold that would stimulate seeding by endogenous cells is attractive, in that it may eliminate the various problems associated with allogenic or xenogenic cells, avoid calcification associated with glutaraldehyde fixation, and potentially provide a biologic matrix with a matrix microenvironment suitable for cellular repopulation. In principle, a synthetic biodegradable scaffold substrate expressing suitable surface ligands to attract and direct the fate of desirable cells would comprise yet another possibility.

Indeed, accumulating evidence suggests that circulating endogenous and other cells can be recruited in vivo to adhere to intravascular sites of injury or prosthetic materials via a pathway that likely mimics the adherence of inflammatory cells to the endothelium during physiological inflammation. Endothelial progenitor cells (EPC) promote endothelial regeneration in dog models by covering implanted Dacron grafts [81] and in human studies by covering the blood-contacting surfaces of implanted ventricular assist devices and homing to stents that have been coated with CD34 antibody (a marker found on EPC and their immature cells) [82,83]. Moreover, recent experimental evidence suggests that the human bone marrow may be a source of hematopoietic progenitor cells contributing VIC to heart valves [84], and bone-marrow-derived myofibroblasts were demonstrated in adult human heart valves [85]. Thus, a potential strategy may be to coat a polymer scaffold in the configuration of a valve with appropriate cell signaling molecules in an effort to encourage EPC and cell adhesion/differentiation. An experiment utilizing decellularized porcine aortic valves containing fibronectin and hepatocyte growth factor suggested that the growth factor enhances early endothelial cell recruitment to, and coverage of, the grafts [86]. There is also evidence that the arterial wall may also be an endogenous source of mesenchymal stem cells that are potentially useful for regeneration and repair [87]. The translation of heart valve tissue engineering and regenerative medicine from the laboratory to the clinical realm has exciting potential but also formidable challenges and uncertainties. A successful tissue-engineered valve must have strength, flexibility, and durability, beginning on implantation and continuing indefinitely thereafter. In addition, the usual paradigm for demonstrating the preclinical and clinical safety and efficacy of medical devices and biologics may need to be altered, particularly owing to the potential for a broader range of unpredictability in, and extended duration and degree of, the interactions of engineered tissue/regenerative therapies with the recipient’s cells and tissues. The major goals will be to (a) develop an understanding of the key mechanisms and consequences of these interactions, including biomarkers for cell and tissue characterization, access to tissues via appropriate and minimally disruptive in vitro and in vivo systems, and assays and tools to characterize the relevant biologic processes and products; and, potentially, (b) to validate early surrogate/proxy endpoints that correlate with clinical success and failure.

The following challenges are representative of the hurdles that must be surmounted before heart valve tissue engineering can be translated from the laboratory to the clinical armamentarium: (a) Animal models are typically used for the testing of heart valves (and other medical devices, drugs, and cell-based therapies), but validation of these models as relevant to human uses will be critical but potentially difficult, especially with respect to autologous versus allogenic cell sources. (b) There is a need to develop guidelines for the characterization and assurance of the quality of an in-vitro-fabricated TEHV for human implantation. (c) The risk/benefit relationships of engineered tissues/regenerative approaches may be unpredictable (especially in early clinical use), in contrast to those of contemporary therapies in which they are often well established. Indeed, in heart valve replacement, clinical progress using conventional approaches over the last half century has been substantial and has engendered a well-established expectation of a certain degree of success (not withstanding the considerable and well-known risks and complications). Thus, acceptance by the medical/surgical community of tissue engineering and regenerative approaches may be slow, and use may be limited initially to well-defined populations with special needs (such as children in whom the results of conventional therapies are less favorable). This perspective is exemplified in an editorial comment by a leading cardiologist who states, “... the ‘next generation’ of PHVs [prosthetic heart valves] must undergo rigorous testing to determine the patient outcomes on long-term follow-up (15 to 20 years);... these PHVs must be documented to confer the same or better outcomes as the ‘older’ good PHVs currently available...” [88]. (d) There is evidence that in vivo remodeling of tissue-engineered products will likely display heterogeneity among individuals in physiological tissue remodeling.
potential as a result of polymorphisms or other variation in key proteins central to remodeling, as has been shown experimentally [89]. Thus, some patients might not appropriately remodel their tissue-engineered structures, potentially leading to failure. In this respect, the principles of pharmacogenetics, which seeks to understand the role of genetics in interindividual variations in drug metabolism, may be applicable to physiologic repair and remodeling processes [90]. Finally, (e) although conventional invasive and/or noninvasive anatomic and functional imaging modalities will certainly be important, to understand, monitor, and potentially control patient variability in wound healing and tissue remodeling in vivo, biomarkers that predict implant success and failure must be identified and validated by assessing tissue healing and remodeling during in vitro and in vivo experiments. Ideally, such biomarkers may be followed in vivo, possibly chemically in the serum or urine [91] or via new modalities of monitoring, such as molecular imaging [92,93]. An important consideration for cell-based therapies is the origin and fate of transplanted cells, particularly to ensure that they are appropriately situated, they retain viability, and they have appropriate phenotypes and function. Recent evidence suggests that gene expression in vivo [94] and the location and function of stem cells can be followed by novel imaging technology [95].

6. Conclusion

There has been considerable and ongoing progress in understanding the pathological basis of and in improving the management of valvular heart diseases. Exciting new frontiers of most interest to contemporary cardiovascular pathology and of potential clinical impact are: understanding of the dynamic pathophysiological basis of valve function and adaptation; the pathologic basis, pathobiology, and genetic aspects of common lesions; developments in innovative endovascular valve substitution and repair; and novel approaches to engineered tissue valve repair and regeneration.

References


