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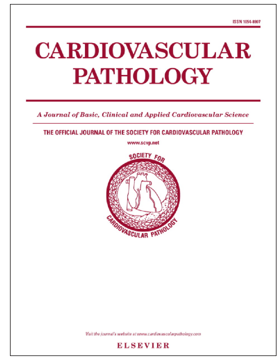

Pathobiology of Cardiovascular Diseases: an Update

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Pathobiology of Cardiovascular Diseases: An Update

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Abstract

This article introduces the Second Special Issue of *Cardiovascular Pathology* (*CVP*), the official journal of the Society for Cardiovascular Pathology (SCVP). This *CVP* Special Issue showcases a series of commemorative review articles in celebration of the 25th anniversary of *CVP* originally published in 2016, and now compiled into a virtual collection with online access for the cardiovascular pathology community. This overview also provides updates on the major categories of cardiovascular diseases from the perspective of cardiovascular pathologists, highlighting publications from *CVP*, as well as additional important review articles and clinicopathologic references.

Keywords: cardiovascular disease; pathology; pathobiology; autopsy; endomyocardial biopsy.

1. Introduction

In 2018, *Cardiovascular Pathology* (*CVP)* published its first ever Special Issue presenting a virtual collection with online access to a series of Consensus Documents produced jointly by the Society for Cardiovascular Pathology (SCVP) and the Association for European Cardiovascular Pathology (AECVP) [1]. Given the popularity of that endeavor, *CVP* is excited to now publish a second Special Issue of *CVP* [2] incorporating the series of 25th anniversary commemorative *CVP* review articles [3–9]. These articles were conceived as a series with the general title of *Pathobiology of Cardiovascular Diseases: Past, Present and Future Perspectives* [3]. The objectives of this second Special Issue of *CVP* are: 1) to assemble the 25th Anniversary commemorative review articles into one cohesive virtual collection with online access for the cardiovascular pathology community; and 2) to broaden the scope of the endeavor by providing updates and commentaries on the major categories of cardiovascular disorders—incorporating important clinical publications while also presenting the viewpoint of cardiovascular pathologists. For access to the Special Issues, go to: https://www.sciencedirect.com/journal/cardiovascular-pathology/special-issue/10W77NHMB8L.

1.1. Basic Anatomy and Physiology

Gross anatomy and histopathology are the mainstays of cardiovascular pathology practice [10]; consideration of the three-dimensional geometry of the heart deserves more attention. Hutchins and colleagues [11,12] published detailed studies of cardiac size, chamber volumes, valve orifices, and shape of the ventricles at autopsy. Differences in the shape of the right and left ventricles when arrested in systole or diastole have been demonstrated [11], and these features should be taken into account in making determinations regarding ventricular hypertrophy and dilation.

More recently, MacIver and colleagues [13,14] have elegantly demonstrated the three dimensional architecture of the heart in relationship to cardiac function; some misconceptions regarding ventricular geometry also were clarified [15]. Recent reviews provide detailed analyses of structure and function of the right ventricle and left atrium in health and disease [16,17]. The challenge of separating physiological hypertrophy from pathological concentric and eccentric hypertrophy also has been addressed [18].

The Human Cell Atlas, a global initiative championed by the Broad Institute [19] (https://www.broadinstitute.org/research-highlights-human-cell-atlas) also promises to shed highly detailed insights into the complex individual genetic and cellular anatomy of the cardiovascular system. Such analyses have already revealed cellular heterogeneity in a host of tissues, elucidating such previously unrecognized cell populations as the pulmonary ionocyte, expressing the bulk of CFTR in lung [20], and distinct subsets of hepatic macrophages [21]. Cardiovascular pathologists will be critical adjuncts and tour guides to the accurate identification, annotation, and exploration of heart and vessel tissues for these analyses.

2. Importance of Core Diagnostic Approaches

2.1. Autopsy

The autopsy remains a procedure of paramount importance in investigation of cardiovascular disease and sudden deaths [22,23]. There is a paradox and a dilemma related to the development of new powerful approaches to obtaining important information from the autopsy while autopsy rates in non-forensic settings, including academic centers, remain distressingly low. Postmortem genetic testing, the so-called molecular autopsy, has become increasingly feasible utilizing next generation sequencing of blood and tissues [22–25]. While fresh specimens are still preferable, utilization of formalin-fixed, paraffin-embedded tissues (FFPPT) is becoming increasingly practicable [26,27]. The emerging importance of the rapid research autopsy leverages powerful technological advances in genetic analyses and organoid cultures with a logistical system for performing autopsies within 6 hours of death [23]. An entire recent issue of the journal *Circulation* was devoted to the application of the autopsy to cardiovascular investigation [28–36].

A major deterrent to routine incorporation of molecular diagnostics in routine autopsy practice is economic. Although the cost of next generation sequencing has decreased substantially, most medical examiner jurisdictions do not have a budget for routine performance of post-mortem genetic testing. A notable exception is the molecular genetic testing laboratory of the Office of the Chief Medical Examiner of New York City which tests for a diverse– but not exhaustive – panel of channelopathy genes in the setting of sudden cardiac death [25]. Secondary, but no less knotty, issues include providing truly informed family consent for post-mortem genetic testing and determining who conveys the results, and how potentially actionable molecular diagnoses are explained to the next-of-kin [37].

2.2. Endomyocardial Biopsy

The development of the technology for endomyocardial biopsy (EMB) in the 1960's was a game-changer in cardiology, enabling pre-mortem cardiac tissue analyses for storage disorders, myocarditis, and sarcoidosis that had not been previously possible [38]. With the dawn of successful cardiac transplantation enabled by the development of calcineurin inhibitors, the EMB surged to even greater importance as the gold standard for evaluating cellular rejection; Billingham and colleagues at Stanford first demonstrated the safety and efficacy of the approach in 1973 [39]. Despite limitations relating to sampling and inter-pathologist variability in diagnoses, the EMB remains the mainstay for surveillance and diagnosis in cardiac rejection; advances in contemporary imaging [40,41] and molecular biomarkers [42] have not made significant inroads on clinical practice in cardiac transplantation.

Thus, EMB interpretation is a core element of contemporary cardiovascular pathology practice; besides evaluating cellular and antibody-mediated rejection (and distinguishing those from ischemic injury, infections, and post-transplant lymphoproliferative disorders), the tissue diagnosis of inflammatory heart disease (myocarditis and sarcoidosis), infiltrative diseases (amyloidosis and lysosomal storage diseases), and toxic injury (chloroquine and anthracyclines) are all critical contributions that arise out of the cardiovascular pathology sign-out [43–47]. Novel tissue biomarkers—evaluable on biopsies—can even be superior to established clinical criteria (and serum analytes) for stratifying risk in heart failure patients [48]. With the increasing application of immune checkpoint inhibitors (ICI) in cancer therapeutics, the EMB has also assumed new importance in the early diagnosis of potentially fatal immune checkpoint inhibitor (ICI) myocarditis [49]. The importance of EMB has been recognized by leading cardiology organizations, and the indications for EMB in various clinical scenarios have been defined [50,51].

Although Pereira et al. [40,41] have stated that contemporary imaging procedures can potentially replace EMB for the diagnosis of some myocardial pathology, EMB remains the standard for validation of imaging techniques, and it uniquely has the potential to yield a tissue diagnosis. Electroanatomic mapping (EAM) guided EMB has the potential to improve test characteristics over conventional fluoroscopy guided EMB [52]. Also, biventricular EMB of the right ventricle (RV) and left ventricle (LV) has been shown to have increased yield of positive findings compared to either selective RV or LV biopsy alone [53].

3. Vascular Diseases

Ladich and colleagues [7][54,55] have provided an overview of vascular diseases reflecting the consensus statements of the SCVP and AECVP on inflammatory and non-inflammatory aortic degenerative disorders. Inflammatory aortic diseases include atherosclerosis, aortitis and periaortitis. Although clinically uncommon, aortitis is increasingly recognized as an important cause of aortic aneurysms and dissections. IgG4-related aortitis is a relatively newly recognized entity in this category. Pathologic diagnosis of specific types of aortitis is based on the pattern of inflammation and associated patient demographic and clinical findings.

Aortic aneurysms are typically subdivided abdominal aortic aneurysms (AAA) versus thoracic aortic aneurysms (TAA), characteristically with different pathologies and etiologies [7]. AAAs are the most common type of aortic aneurysm, and are attributed to underlying atherosclerotic pathology [7]. Some atherosclerotic aneurysms involve both the thoracic and abdominal aorta, i.e., throraco-abdominal aortic aneurysms (TAAA) [56]. Such atherosclerotic aortic aneurysms have distinct risk factors and genetic predisposition compared to usual atherosclerotic disease [57,58].

The causes of TAA vary depending on the site of involvement, but medial degeneration is a common pathologic substrate, regardless of etiology [7,55]. Compared to TAAA and AAA, thoracic aneurysms are more commonly associated with systemic hypertension, likely causing compromise of the *vasa vasorum* perfusion of the media; patients with bicuspid aortic valves are also prone to root dilation, attributed to a combination of abnormal flow through the bicuspid valve, and subtle genetic effects on matrix synthesis that may be associated with the bicuspid valve development. Mutations that affect transforming growth factor-β (as in Marfan's and Loeys-Dietz syndromes), primary matrix mutations (e.g., Ehlers-Danlos III), and endarteritis obliterans of the *vasa vasorum* vessels (luetic aortitis) are all less common causes of TAA—but nevertheless important (because they are amenable to therapeutic interventions). There is a genetic basis for most aortic aneurysms with prominent medial degeneration [59], and aortopathy is also a feature of several forms of congenital heart disease [60,61].

Vascular calcification is now recognized as a highly regulated biological process [7]. Calcification may involve the intima associated with atherosclerotic pathology or in the media secondary to metabolic disease. Rarely, vascular calcification develops as a manifestation of genetic disorders.

4. Atherosclerosis and Ischemic Heart Disease

4.1. Atherosclerosis

Pathologists have made landmark contributions to our understanding of the pathogenesis of atherosclerosis [62–64].The resultant comprehensive construct advanced by Russell Ross and colleagues - the response to injury theory of the pathogenesis of atherosclerosis - reflects a synthesis of extensive experimental evidence and correlation with disease expression in humans [65]. This theory posits that atherosclerosis develops as an inflammatory response of the arterial wall that is initiated by endothelial perturbation (damage) induced by multifactorial, chronic (repetitive) chemical and hemodynamic injury, and is followed by complex secondary changes in the evolving lesions [66–68]. Thus, fundamentally, atherosclerosis is conceived as a specialized inflammatory disease, and atherogenesis as a process driven by inflammation and innate and acquired immunological mechanisms [69–71]. In this regard, the beneficial effects of the statins are likely a consequence of their anti-inflammatory pleotropic effects as much as from their lipid-lowering effect. Other interventions aimed at affecting inflammatory and immunological drivers of atherosclerosis are also garnering increased interest [72].

It also should be noted that the current iteration of the response to injury theory does not account for observations interpreted as early lesions developing as cell clones in the intima of blood vessels. The clonal origin hypothesis remains the subject of investigation and speculation [73]. Remarkably, the expansion of myeloid cell clones in geriatric bone marrow (so-called clonal hematopoiesis of indeterminate potential or CHIP) has been correlated not only with an increased risk of hematologic malignancy (not too surprising), but also with atherosclerotic disease risk (extremely surprising) [74]. The relationship may be attributable to the selective expansion in inflammatory monocyte-macrophage lineages producing mediators such as interleukin-1 (IL-1) [75]. This becomes extremely clinically relevant in that IL-1 blockade has significant benefits against atherosclerotic disease burden and complications [76].

In the cardiovascular pathology community, the characterization and classification of lesions of atherosclerosis, arteriosclerosis, arteriolosclerosis and vascular calcification continue to be discussed [77].

4.2. Ischemic Heart Disease and Acute Myocardial Infarction

Buja and Vander Heide [5] provided a comprehensive perspective on the pathobiology of ischemic heart disease: past, present and future. Topics covered included basic pathobiology of coronary artery disease, basic pathobiology of myocardial ischemic injury and acute myocardial infarction (AMI), importance of infarct size, the first phase of approaches to limit infarct size, basic pathobiology of myocardial reperfusion, clinical reperfusion therapy, myocardial stunning and hibernation, ischemic preconditioning, new insights into pathobiology with a focus on mitochondria, recent clinical trials for preservation of ischemic myocardium and approaches to myocardial repair and regeneration [5,78]. Major knowledge gaps and future directions for ischemic heart disease (IHD) also were articulated (Table 1).

There also has been an evolution in the thinking regarding the relationship of coronary atherosclerosis to the development of an acute coronary syndrome (ACS) [79]. The traditional view proposes that the clinical horizon of acute IHD occurs when progressively accumulating atherosclerosis causes critical luminal compromise - usually involving multiple plaque formation. However, in the vulnerable plaque model, acute plaque change dominates the clinical decompensation. Thus, an acute ischemic event is not closely linked to the severity of coronary atherosclerosis (due to positive vascular remodeling – the Glagov effect) but rather is triggered by the development of instability and thrombosis of a vulnerable plaque that is frequently not critically stenotic. A modulating perspective is provided by the atherosclerotic plaque burden hypothesis: an individual patient may have multiple vulnerable coronary plaques; instability and thrombosis of a single vulnerable plaque may or may not trigger an acute ischemic event; the total burden of atherosclerotic disease is of major importance in leading to an ACS. This hypothesis reflects the complexity between the relationship of thrombosis of an atherosclerotic coronary artery and AMI. Indeed, determination of the link between coronary thrombosis and acute myocardial infarction (AMI) has a long and convoluted history [63,80], although a causal role for coronary thrombosis has now been firmly established [5,78–80].

Percutaneous coronary intervention (PCI) with angioplasty coupled with coronary stent placement is a well-established approach for managing ACS. Coronary stents have evolved from bare metal stents (BMS) to drug eluting stents (DES) to fully bioresorbable scaffolds (BRS).

Virmani and colleagues [81–84] have performed extensive studies over more than a decade to characterize the vascular responses to implanted stents of various types and to elucidate clinical correlates of the pathobiology occurring in the stented segments . The pathological findings regarding vascular responses to BMS and DES clearly point to the importance of endothelization of the stented neointima; less than complete and effective endothelial covering will lead to adverse outcomes, including late thrombosis [85]. Adverse reactions to stents involve multiple interrelated mechanisms including stent characteristics, procedural factors, individual susceptibility influenced by genetic predisposition and clinical factors, and the inflammatory response. This complex milieu can result in delayed or impaired re-endothelialization, vascular perforation, or even focal aneurysm formation. Continued attention to the basic pathobiology of vascular responses to injury and interventions is of paramount importance in developing improved therapeutic interventions and optimal clinical outcomes [85].

Because of its importance in clinical decision making, documentation of the severity of coronary atherosclerosis has been a major focus of clinical research and cardiology practice for many years. Stenosis severity has traditionally been assessed by direct angiographic visualization or functionally through measurements of fractional flow reserve (FFR) [86]. For both clinical and research purposes, histopathological assessment is important for correlation with angiographic and other assessments of the nature and extent of coronary artery disease. A variety of approaches have been used [87–89].

The array of diagnostic modalities has grown to include qualitative coronary angiography, quantitative coronary angiography, computed tomographic angiography, magnetic resonance imaging angiography, intravascular ultrasound (IVUS), and optical coherence tomography (OCT) [90–93]. A focus of ongoing development work is fluorescence lifetime imaging (FLIm). Various imaging modalities are purported to provide “virtual histology” of the coronary tree [90]. However, histopathology remains essential for validation of the accuracy of the imaging procedures [94-97].

An improved method for mapping and registration of coronary arteries in longitudinal view on histopathology has recently been developed; this involves a three-dimensional alignment procedure for postmortem quantitative coronary plaque analyses [89]. This new procedure has been applied to calcified coronary plaque analyses comparing post-mortem computed tomography angiography (PMCTA), optical coherence tomography (OCT) and histopathology. In 338 specimens, the 3D fusion approach, aligning the images of PMCTA and OCT with histopathology as the gold standard allowed for a slice-based comparison of the different modalities. The results showed that PMCTA overestimates the calcified plaques while OCT underestimates these, compared to what is seen through the microscope.

Acute myocardial infarction has now been classified into five types (Table 2) [98–100]; the scheme takes into account the advent of high sensitivity troponin measurements and the underlying pathophysiology. Thus, a distinction is made between myocardial injury with elevated troponin due to non-ischemic causes (e.g., myocarditis) versus type 2 acute myocardial infarction with elevated troponin and clinical evidence of myocardial ischemia. Both may be associated with guarded prognosis. However, utilizing strict criteria, type 2 acute myocardial infarction is currently being over diagnosed [101]. We recommend that pathologists take this classification of AMI into account in evaluating and reporting AMIs along with the traditional characterizations regarding location, extend and age of the lesions.

5. Sudden Cardiac Death (SCD), including Sudden Arrhythmic Death (SAD)

5.1. Basic Structure-Function Relationships of the Electrical Heart [4,8]

Saffitz and Corradi [4] have provided a perspective on the evolution of our understanding of how altered tissue structure determined by classical pathology contributes to the pathogenesis of major heart rhythm disorders. They reviewed the remarkable advances in our understanding of the genetic basis for cardiac rhythm disturbances and the elucidation of fundamental mechanisms of abnormal conduction and impulse formation. Ottaviani and Buja [8] have provided a complementary review of advances in the study of anatomic and pathological changes of the conduction tissue in relationship to age of onset of sudden cardiac death (SCD) .

SCD is defined as the unexpected death without an obvious non-cardiac cause that occurs within one hour of witnessed onset of symptoms (established SCD) or within 24 hours of unwitnessed onset of clinical manifestations (probable SCD). The incidence in the USA is reported as 69/100,000 per year [8]. SCD appears in 13.4% of death certificates. The incidence of SCD has a peak in infancy, decreases in older children, then in adults it increases exponentially with age, surpassing the risk for infants by the age of 40 [102]..

5.2. Perinatal and Infant Deaths [8]

The focus of investigation of perinatal deaths has been expanded based on convincing evidence for a continuum involving sudden infant death syndrome (SIDS), sudden perinatal unexpected death (SPUD), and sudden intrauterine death syndrome (SIUDS). SIDS, also called crib death, is the most frequent form of death in the first year of life, striking one baby in every 1,700–2,000. Despite advances in maternal-neonatal care, SIUDS has an incidence 6-8 times greater than that of SIDS [103–105]. The SIDS–SIUDS complex [105] has been defined as the sudden death of a fetus after the 25th gestational week or infant under one year of age which is unexpected by history and remains unexplained after a thorough case investigation, including examination of the death scene, performance of a general autopsy and examination of the placenta, umbilical cord, and membranes. A complete and careful autopsy examination is required to rule out various causes and to document subtle changes associated with unexplained perinatal and infant deaths. An evolving understanding of the pathogenesis of SIDS and related conditions is based on postulated cardio-respiratory and respiratory-reflexogenic mechanisms, related to minute lesions of the central nervous system, particularly of the brainstem, together with involvement of the cardiac nervous and conduction system. Frequent congenital abnormalities, are likely morphological substrates for SIDS–SIUDS; these are mainly represented by alterations of the cardiac conduction system, such as accessory pathways and abnormal resorptive degeneration, along with hypoplasia, agenesis or neuronal immaturity of vital brainstem structures [8,103–105]. A novel hypothesis has recently been advanced linking SIDS to $C0^2$ retention [106].

5.2. Sudden Death of Adolescents and Adults [5]

SCD includes deaths due to non-arrhythmic, mechanical causes, such as ruptured acute myocardial infarction, and deaths due to fatal ventricular arrhythmia, i.e., sudden arrhythmic death (SAD) and sudden arrhythmic death syndrome (SADS) [107,108] . Dysfunctions of the cardiac conduction and autonomic nervous systems are known to contribute to SCD pathogenesis, as are ventricular arrhythmias triggered by ectopic foci in hypertrophied hearts and those with acute ischemia [4,8].

Guidelines have been published for autopsy investigation of sudden cardiac death [109,110]. Many cases have ischemic heart disease as the pathological substrate [111]. Other causes are more common in younger individuals including coronary artery anomalies, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy [108]. Acute aortic dissection is reported to have an outside-of-hospital death rate of 20% [112].

Genetic factors contributing to SCD and SADS are now recognized to be important [113,114]. Subjects with primary arrhythmias, including prolonged QT syndromes and channelopathies, typically have hearts with no gross or histopathological findings. The only pathological finding in other subjects may be significant left ventricular hypertrophy. Left ventricular hypertrophy is a well-documented, independent risk factor for SCD [115-118]. Post-mortem genetic testing can contribute significant information in determining the substrate for SCD and SADS [24,25,30–35].

6. Congenital Heart Disease

The in-depth characterization of the anatomic pathology and pathophysiology of congenital heart disease (CHD) contributed by expert pathologists has led to accurate early diagnosis and effective surgical treatments for CHD [104,119,120]. Advances also have been made in understanding the developmental biology and molecular pathogenesis of CHD [121–123]. A symposium on CHD has been published in this journal addressing anatomic and pathophysiological classification and postoperative pathology of CHD as well as challenges and opportunities for CHD in adults [124–127].

Specific environmental risk factors, such as maternal smoking, air and water pollution, food concentration, pesticides, etc., can interact with the individual genetic constitution in complex ways, which may lead to polymorphisms and/or mutations of specific diseases leading to abnormal cardiac morphogenesis and CHD. Success in diagnosis and surgical correction of CHD has led to the development of the new subspecialty of adult congenital heart disease. Multidisciplinary teams, including obstetricians, pediatric and adult cardiologists, anesthesiologists, cardiac surgeons, and above all, cardiovascular pathologists, are essential for understanding, managing and treating CHD to provide optimal outcomes. Further studies are needed to identify more precise etiologies, preventive measures, and standardized diagnostic and therapeutic guidelines, to improve the survival and quality of life for CHD in fetuses, children, young adults and geriatrics [119,120] .

7. Valvular Heart Disease

Schoen and Gotlieb have reviewed major advances in the understanding of the structure, function, and biology of native valves and the pathobiology and clinical management of valvular heart disease [6,128]. In high income countries today, the two major causes of clinically significant acquired valvular disease are degenerative valve diseases led by calcific aortic valve disease (CAVD) and myxomatous mitral valve prolapse disease (MVP) [6,128]. Conversely, in low income countries, rheumatic heart disease remains a major problem [129,130]. CAVD leads to aortic stenosis (AS)/calcific aortic stenosis (CAS) [131,132]. MVP leads to mitral valve prolapse with variable mitral regurgitation, and in syndromic form, susceptibility to potentially fatal arrhythmias [133,134]. Regarding pathogenesis, transcriptional regulation of heart valve development and disease is being defined, as is the role of hemodynamics and cellular and subcellular dynamics of the valve components [6,128,135–138]. Perturbations of valvular interstitial cells (VIC) figure prominently in the pathobiology of both conditions [6,128].

The two categories of prosthetic valves utilized in valve replacement are mechanical valves and tissue valves [6,128]. Open chest valve replacement under cardiopulmonary bypass is increasingly being superceded by minimally invasive catheter-based valve replacement procedures, particularly transcatheter aortic valve implantation (TAVI). Similarly, total mitral valve replacement is being supplanted when possible by mitral valve sparing procedures, including the use of various mitral valve clip devices. Pathology associated with these devices and procedures have been described [6,10,128,139–144].

8. Cardiomyopathies and Myocarditis

The cardiomyopathies, or heart muscle diseases, received formal recognition and classification by the World Health Organization in 1980 [145]. Subsequently, research has led to more refined definitions and increased understanding of these entities [146–148]. Working groups of the American Heart Association and the European Society of Cardiology have developed complimentary classifications of the cardiomyopathies which recognize primary genetic, primary acquired and mixed etiologies of cardiomyopathies [149–151]. These principles are recognized in an approach linking etiologic to clinicopathological features (Figure 1). A cardiomyopathy compendium was published in the September 15, 2017 issue of *Circulation Research* presenting important advances in the pathobiology, pathogenesis, clinical recognition, diagnostic imaging, and natural history of these conditions [25,152–162].

9. Cardiac Repair and Regeneration

The field of cardiac regenerative medicine has developed over the past decade based on intense interest in the biology and potential therapeutic applications of myocardial and vascular stem cells [163]. There was an initial siren call that such preparations could bypass the non-regenerative properties of mammalian myocardium and pointed tantalizingly to the potential for significant myocardial restoration and sustained functional improvement following acute or chronic injury [164–166]. The rationale for cell-based therapy is based on an overly optimistic goal that this therapy can effectively modulate the basic pathobiology of the myocardium during stages of compensatory hypertrophy and failure in response to stressors, as elucidated by detailed quantitative studies conducted by pathologists and experimental biologists. However, recent developments have tempered much of the initial enthusiasm for cardiac cell-based therapy with a recalibration of expectations.

Millions of dollars have been expended on clinical trials of cardiac stem cell therapy yielding unconvincing results regarding the efficacy of stem cell therapy to produce sustained improvement of cardiac structure. The clincal and experimental studies show that mesenchymal stem cells (MSCs) and cardiac-derived stem cells (CSC) do not impart signficant remuscularization of infarcted myocardium and are associated with only modest short-term enhancement of cardiac function at best More promising candidates for cell based therapy for ischemic heart disease are cardiomyocytes derived from embronic stem cells (ESC) or inducible pleuripotential stem cells (iPSC), but the durablility and arrhythmogenicity of these preparations remain concerns [163–166]. The same reservations apply to the proposed utilization of various tissue engineering methods for application of stem cells to the heart [167].

Regarding the underlying issues of regenerative capacity and the mechanism(s) responsible, a strong consensus has emerged that the limited regenerative capability of mamalian myocardium is primarily a consequence of low level re-entry of mature cardiomyocytes into the cell cycle, and not, as previously asserted on the differentiation of stem cells into cardiomyocytes [168]. This consensus is grounded in detailed quantitative studies conducted by pathologists and experimental biologists [163–166].

Based on the overall poor results and at best modest cardiac functional improvement with exogenous stem cell therapy, further investment of human and financial resources in such therapy does not currently appear warranted. However, investigating the molecular basis for the limited replicative capacity of cardiomyocytes likely represents a more fruitful line of investigation for potential therapeutic intervention [123,169–171]. The current bottom line is that the ability of exogenously administered stem cells to produce biologically and clinically significant enhancement of myocardial repair – much less regeneration – after injury remains unproven; cardiovascular pathologists can help clear the murkiness of the field by providing rigorous tissue evaluations [164,172].

10. Heart Failure

Halushka, Mitchell and Padera [9] reviewed the concepts and treatments of heart failure from the last 25 years, highlighting some of the new directions in non-pharmacologic therapy. Previous reports in this journal have focused on the pathophysiology and pathobiology of heart failure as well as biomarkers for monitoring this condition [173–177]. Whether acute or chronic, heart failure remains a major health care crisis affecting over 6 million Americans and over 23 million people worldwide. Roughly half of those affected will die within 5 years, and the annual cost exceeds $30 billion in the US alone[102]. Although medical therapy has made some modest inroads in partially stemming the heart failure tsunami, there remains a significant population for whom medication is unsuccessful or has ceased being effective; such patients can benefit from heart transplantation or mechanical circulatory support [9]. Indeed, in the past quarter century (and as covered in *Cardiovascular Pathology* over those years), significant improvements in clinicopathologic understanding [176,177] and in engineering design have materially enhanced the toolkit of options for such refractory patients. Mechanical devices, whether total artificial hearts or ventricular assist devices, have been reengineered to reduce basic wear and tear, thus extending device longevity, while minimizing thromboses and other complications. Transplant survival has also been extended through a better comprehension of and improved therapies for transplant vasculopathy and antibody-mediated rejection.

Recent developments have led to a convergence of cardiovascular medicine and oncology, and the emergence of a new cardio-oncology subspecialty [178]. Significantly, excluding demise due to the malignancy itself, treatment-induced adverse cardiovascular events are the leading cause of death in cancer patients. In calculating the relative risks and benefits of anti-cancer therapy, it is therefore important to consider the morbidity and mortality associated with antitumor therapy itself. Chemotherapy, targeted therapies, immune checkpoint blockade, and radiation therapy can all adversely impact cardiac function; their effects can also be synergistic. Consequently, it is important that possible therapeutic side effects be recognized and effectively controlled. Glass and Mitchell [178] have reviewed the mechanisms and histopathologic findings associated with common forms of potentially cardiotoxic cancer therapy including anthracyclines, tyrosine kinase inhibitors, and most recently immune checkpoint inhibitors [49]. Although the histologic findings in many cases are nonspecific, in the appropriate clinical context, therapeutic cardiotoxicity can be inferred and the treatment approach refined appropriately.

11. Tumors of the Heart and Blood Vessels

Tumors of the heart and blood vessels, while uncommon, continue to fascinate pathologists. This is reflected in the large number of case reports and review articles published in *CVP* [3]. These reports often feature unusual features and presentations of primary cardiac tumors as well as the more common metastatic tumors. The review articles include several longitudinal experiences of major medical centers [179–187]. Collectively these articles provide a comprehensive analysis of tumors of the heart and blood vessels. In recent years, a major monograph and an updated atlas on this topic have been published [188,189].

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Introduction

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Table 1. Ischemic heart disease: Major knowledge gaps and future research directions

Gaps	Research directions
Reliable clinical identification of vulnerable plaques leading to acute coronary syndrome (ACS) and understanding of the underlying initiating mechanisms are inadequate.	Continued work is needed on noninvasive methods for distinguishing different types of plaques and identifying initiating mechanisms in clinical situations.
Successive generations of coronary stents have resulted in long-term patency of previously stenotic segments of coronary arteries; however, segments with drug-eluting stents are subject to late thrombosis and atherosclerosis.	Develop new strategies to retard intimal thickening due to proliferation of myofibroblasts and to promote endothelial regeneration.
The progression from reversible to irreversible cardiomyocyte injury involves oncotic and apoptotic pathways, but the complex interactions are not fully understood.	Further define these pathways while investigating possible targets for therapeutic interventions.
While components of the trigger phase of IP have been well established, the ultimate effector of the protective effect of preconditioning has not been determined.	Continue to investigate biochemical and molecular mechanisms of the mediator/effector phase of IP.
While experimental studies have provided evidence that a number of pharmacological agents and pathophysiological interventions can exert protective effects on the evolution of myocardial infarction, application of these approaches in clinical trials have yielded generally equivocal results, including the most recent trials combining pharmacological agents and conditioning protocols.	Continue to refine the design of clinical trials with the aim of extending proof of principle into practical clinical application for improvement in morbidity and mortality of patients with IHD.
While advances in the last 50 years have resulted in major reduction in the morbidity and mortality from ACS, there has been a progressive increase in the incidence of patients with chronic IHD requiring advanced therapies	Since progression of chronic heart failure is caused by progressive pathological remodeling of the myocardium, further research is needed to gain a better understanding of pathological remodeling and to develop approaches to modulating its development and progression.
While a rationale for cell-based therapy for salvage and repair of ischemic myocardium and reversal of chronic heart failure has been advanced, the clinical trials of such therapy have yielded only modest results particularly in relationship to consideration of return on investment.	Develop new paradigms with a stronger experimentally grounded basis for continuation of cell-based therapeutic interventions.

ACS, acute coronary syndrome; IHD, ischemic heart disease; IP, ischemic preconditioning

Adapted from: Buja LM, Vander Heide RS. Pathobiology of ischemic heart disease: past, present and future. Cardiovasc Pathol 2016;25:214–20. doi:10.1016/j.carpath.2016.01.007 [5].

Table 2. Clinical classification of different types of myocardial infarction

Infarction Types	Clinical Features
Type 1 MI	Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2 MI	Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3 MI	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4A MI	Myocardial infarction associated with PCI
Type 4B MI	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5 MI	Myocardial infarction associated with CABG

MI, myocardial infarction; LBBB, left bundle branch block; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Adapted from: Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53. doi:10.1161/CIRCULATIONAHA.107.187397 [98].

Figure Legend

Figure 1. Combined etiologic, molecular and pathologic classification of cardiomyopathies. Modified from:

Thiene G, Basso C, Calabrese F, Angelini A, Valente M. Twenty years of progress and beckoning frontiers in cardiovascular pathology: cardiomyopathies. Cardiovasc Pathol 2005;14:165-9 doi:10.1016/j.carpath.2005.03.008 [146].

Poller W, Kühl U, Tschoepe C, Pauschinger M, Fechner H, Schultheiss H-P. Genome–environment interactions in the molecular pathogenesis of dilated cardiomyopathy. J Mol Med (Berl) 2005;83:579–86. doi:10.1007/s00109-005-0664-2 [147].

Figure 1. Combined etiologic, molecular and pathologic classification of cardiomyopathies

Etiology

Primary gene mutation

Primary environmental acquired insult – virus, drug, toxin, stress

Gene-environment interaction

Molecular Pathotype	**Pathophysiological Type**
Cytoskeletal CMP (Sarcolemma/sarcomere linkage)	Dilated CMP Non-compaction LV CMP
Cell Junction CMP	ARVD/C, cardiocutaneous syndromes
Sarcomeric CMP	Hypertrophic CMP and Restrictive CMP
Ion Channel CMP	Long and short QT syndromes, Brugada syndrome, catecholaminergic polymorphic VT

CMP, cardiomyopathy; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy: LV, left ventricle; VT, ventricular tachycardia.

Modified from:

Thiene G, Basso C, Calabrese F, Angelini A, Valente M. Twenty years of progress and beckoning frontiers in cardiovascular pathology: cardiomyopathies. Cardiovasc Pathol 2005;14:165-9 doi:10.1016/j.carpath.2005.03.008 [146].

Poller W, Kühl U, Tschoepe C, Pauschinger M, Fechner H, Schultheiss H-P. Genome–environment interactions in the molecular pathogenesis of dilated cardiomyopathy. J Mol Med (Berl) 2005;83:579–86. doi:10.1007/s00109-005-0664-2 [147].

Conflict of Interest Statement

I as well as my coauthors, Dr. Ottaviani, and Dr. Mitchell, have nothing to disclose and no conflicts of interest regarding the content of this manuscript.

Highlights

This article introduces the Second Special Issue of *Cardiovascular Pathology* (*CVP*), the official journal of the Society for Cardiovascular Pathology (SCVP).

This *CVP* Special Issue showcases a series of commemorative review articles commemorating the 25th anniversary of *CVP* originally published in 2016.

This overview also provides updates on the major categories of cardiovascular diseases from the perspective of cardiovascular pathologists.

Combined Etiologic, Molecular and Pathologic Classification of Cardiomyopathies

Etiology

Primary gene mutation

Primary environmental acquired insult – virus, drug, toxin, stress

Gene-environment interaction

Molecular Pathotype	**Pathophysiological Type**
Cytoskeletal CMP (Sarcolemma/sarcomere linkage)	Dilated CMP Non-compaction LV CMP
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CMP, cardiomyopathy; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy: LV, left ventricle; VT, ventricular tachycardia.

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