Cardiovascular Pathology 25 (2016) 149–157

Contents lists available at ScienceDirect

Cardiovascular Pathology

Pathobiology of Cardiovascular Diseases: Past, Present and Future Perspectives (*CVP* 25th Anniversary Special Review Article)

The electrical heart: 25 years of discovery in cardiac electrophysiology, arrhythmias and sudden death

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ARTICLE INFO

Article history:
Received 25 September 2015
Received in revised form 23 November 2015
Accepted 26 November 2015

Keywords:
Cardiac electrophysiology
Sudden death
Ventricular tachyarrhythmias
Atrial fibrillation

ABSTRACT

This review summarizes progress in the fields of cardiac electrophysiology, arrhythmias and sudden death made in the 25-year interval between 1992 and 2016 during which time *Cardiovascular Pathology* has been published. Organized along clinical lines, it considers the major heart rhythm disorders underlying atrial, atrioventricular and ventricular arrhythmias, and sudden cardiac death. There is a strong focus on the remarkable advances in understanding the genetic basis for cardiac rhythm disturbances and elucidating fundamental mechanisms of abnormal conduction and impulse formation. During this 25-year period, our understanding of how altered tissue structure (classical pathology) contributes to arrhythmias and sudden death has undergone continuous refinement as new insights have been gained about arrhythmia mechanisms and the dynamic interplay between anatomic substrates and triggers of the major heart rhythm disorders.

1. Introduction

The 20th century saw a dramatic increase followed by a dramatic decrease in the incidence of heart disease deaths in the US and Europe, attributable largely to the epidemic acceleration and then the marked decline in the incidence of coronary atherosclerosis [1]. As many as half of heart disease deaths in the 20th century were sudden (the exact proportion is difficult to determine accurately), presumably caused by lethal ventricular tachyarrhythmias. Cardiac pathologists have fulfilled a vital role in carefully documenting the extent and distribution of coronary atherosclerosis and myocardial infarction at autopsy, but it has remained challenging for us to explain the pathology of sudden cardiac death. Although the great majority of sudden death victims exhibit coronary artery disease and variable patterns of ventricular remodeling related to myocardial ischemia and infarction, the same pathologic features are present in so many other subjects who did not die suddenly. Occasionally, sudden death may occur in a young individual whose heart appears entirely normal at autopsy. It was only in the latter 2 decades of the 20th century that the pathology of sudden cardiac death could be understood in the context of cardiac electrophysiology. During this remarkably fertile period, the field of clinical cardiac electrophysiology was born. It has since undergone explosive growth and maturation. Previously untreatable conditions such as Wolff-Parkinson-White syndrome can now be cured through precise mapping and ablation procedures. Recurrent ventricular tachycardias can be similarly treated, and sophisticated implantable defibrillators now save the lives of many patients at high risk of sudden death. In recent years, focus has shifted from ventricular to atrial arrhythmias in recognition of the enormous public health burden associated with atrial fibrillation. In 1990, 2 years before *Cardiovascular Pathology* (*CVP*) made its debut, the first mutation underlying a human cardiomyopathy (*MYH7* in hypertrophic cardiomyopathy) was defined [2]. Since then, breathtaking progress has been made in understanding the genetic and molecular basis of the non-ischemic cardiomyopathies, not to mention the "ion channelopathies", a term which, at the time *CVP* first appeared, had not yet been coined, and such conditions were recognized solely on the basis of ECG changes and clinical features. Elucidation of Mendelian disease alleles in familial sudden death syndromes has also greatly advanced research on the fundamental genetics and molecular biology of normal cardiac electrophysiology. The recent advent of genome-wide screening has opened new opportunities to decipher genetic determinants of far more common arrhythmias such as atrial fibrillation. Now, in the 25th year of *CVP*, the role of the pathologist remains as important as ever in explaining how complex heart rhythm disturbances happen and what can be done to treat or prevent them. Here, we briefly review a quarter century of discovery in the "electrical heart". Throughout this review, we use the first and last names of individuals we consider to be the true pioneers and whose seminal work has driven progress in this field.

2. The pathology of cardiac arrhythmias and sudden death

Historically, pathologists have contributed to the field of cardiac electrophysiology mainly through the careful identification and

Funding: There is no funding information for this paper.
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http://dx.doi.org/10.1016/j.carpath.2015.11.005
1054-8807/

description of normal anatomic structures responsible for impulse generation (sinus node [3]) and impulse distribution and conduction (atrioventricular node [4], bundle of His [5], Purkinje fibers [6]), or abnormal structures responsible for aberrant patterns of electrical activation (for example, the bundle of Kent [7] or Mahaim fibers [8] in pre-excitation syndromes, or anatomic lesions of the atrioventricular node in congenital or acquired heart block [9,10]). During the last 25 years, pathologists have helped define the pathology of the major cardiac arrhythmias and sudden death in the context of contemporary tools of clinical electrophysiology. To a large extent, our attention has been directed to specific regions of the heart guided by increasingly sophisticated electrophysiological mapping procedures used to pinpoint sites of origin of arrhythmias and define pathways of arrhythmia circuits. With the advent of arrhythmia ablation procedures, a new field of pathology has emerged focused on mechanisms of tissue injury and correlation of anatomic features with clinical outcomes [11]. What follows is a brief review of advances in understanding the major cardiac arrhythmias over the past 25 years arranged in roughly chronological order. Because of the scope and complexity of this subject, it was necessary that we forego consideration of many important topics including sudden infant death syndromes, resuscitation/defibrillation from cardiac arrest, and life style changes to reduce risk of cardiac arrhythmias and sudden death.

2.1. Atrioventricular arrhythmias

Atrioventricular arrhythmias are those that involve both atrial and ventricular myocardium, and in which the arrhythmia circuit traverses the atrioventricular (AV) junction. The most common types of atrioventricular arrhythmias are AV nodal reentrant tachycardia or Wolff-Parkinson-White syndrome. While atrial fibrillation (AF) with a rapid ventricular response might be considered to be an atrioventricular arrhythmia, the arrhythmia circuit only involves the atria and not the ventricle(s). The first closed-chest ablation of the atrioventricular junction was performed in 1982 in patients with drug-refractory supraventricular arrhythmias (most had atrial fibrillation and rapid ventricular response) [12,13]. The earliest catheter ablations by radiofrequency energy of accessory atrioventricular pathways in Wolff-Parkinson-White syndrome were reported in 1991 [14,15]. These early efforts made it possible to cure what were otherwise potentially life-threatening supraventricular arrhythmias for which previous drug therapy was often ineffective. Advances in high resolution mapping in patients with AV nodal reentrant tachycardias revealed bidirectional pathways within the AV junction which, in most patients, involved an anterograde limb of the circuit that conducts slowly (thereby enabling reentry) and a retrograde limb that conducts rapidly [16]. Identification of these functionally important compartments of the AV junction facilitated studies of their microscopic anatomy and expression profiles for proteins relevant in impulse propagation such as ion channel proteins and connexins [17]. Pertinent papers published in *CVP* on this general topic include reports on cystic tumor of the atrioventricular node [18] and analysis of AV nodal artery variants [19].

2.2. Ventricular arrhythmias and sudden cardiac death

Historically, investigation of sudden cardiac death at autopsy has included attempts to identify relevant pathologic changes in the cardiac conduction system (sinus and AV nodes, His bundle, Purkinje network). Pathologists have made important contributions in describing the normal microscopic anatomy of this system and in identifying a large array of developmental and acquired structural changes that can reasonably be linked to electrocardiographic abnormalities and sudden death [20–22]. While a detailed analysis of the cardiac conduction system at autopsy may provide critical information explaining some cases of sudden death, such efforts provide only limited insights into arrhythmia mechanisms and structure/function relationships in the majority of sudden deaths. This is because most lethal ventricular arrhythmias originate in, and follow circuits confined to, the ventricular myocardium itself.

In the common settings of ischemic heart disease and chronic heart failure due to hypertension or valvular heart disease, these arrhythmias generally arise as a result of triggered activity and/or reentry [23]. In the former mechanism, a premature ectopic impulse is generated before or after full repolarization of a cell or group of cells in which abnormal ionic conditions prevail. Typically, there are no specific anatomic features to distinguish such cells from those with normal cellular electrophysiology. By contrast, reentry depends on abnormal impulse propagation (conduction) and, in most cases, arises in structurally remodeled ventricular myocardium. It is in this context that the concept of "anatomic substrates" of ventricular tachycardia has evolved. Here again, pathologists have made major contributions in meticulously describing the wide range of structural abnormalities that constitute anatomic substrates of ventricular arrhythmias. Collaborations between pathologists and cardiac electrophysiologists during the last 25 years have given rise to the general concept that virtually any structural abnormality of the ventricular myocardium can alter cell-cell impulse conduction via gap junctions, disturb temporal and/or spatial patterns of electrical activation of the heart, and increase the likelihood of ectopic impulse formation. The most common and important of these anatomic substrates occur in patients with ischemic heart disease and include necrosis, hypertrophy and/or degenerative changes in cardiac myocytes, and fibrosis (both interstitial and replacement). We have gained insights into how such changes in microscopic anatomy impact cellular and whole heart electrophysiology [24,25]. We have also identified characteristic substrates associated with specific types of heart diseases such as myocyte disarray in hypertrophic cardiomyopathy and fibro-fatty scar tissue in arrhythmogenic cardiomyopathy. There is little doubt that these substrates play a major role as determinants of risk of sudden death in these non-ischemic heart muscle diseases. Nevertheless, it must be emphasized that lethal arrhythmias arise as a consequence of complex interactions between acute triggers and relatively fixed substrates. In fact, the majority of patients with coronary artery disease or a non-ischemic cardiomyopathy whose hearts are remodeled do not experience potentially lethal ventricular arrhythmias. Autopsy pathologists are, therefore, acutely aware of the relatively non-specific nature of these anatomic changes.

The early 1980s saw the first catheter ablation of recurrent ventricular tachycardia [26], and advances in intracardiac mapping and new arrhythmia surgical procedures made it possible to study the pathology of sites of origin and arrhythmia circuits in patients with healed infarcts and recurrent ventricular tachycardia [25]. Since then, real-time 3-dimensional magnetic electroanatomical and non-contact endocardial mapping systems have been used to identify and ablate ventricular tachycardias in patients with ischemic and non-ischemic cardiomyopathies [27,28]. In a related engineering tour de force, the "inverse problem" of electrocardiography was solved by Yoram Rudy and his group in 2004 to allow non-invasive, high-resolution mapping of electrical activity on the epicardial surface of the heart by computational processing of electrical potentials recorded on the body surface, a technique called electrocardiographic imaging, or ECGI [29]. This approach may eventually replace invasive mapping techniques in diagnosing and managing arrhythmias.

In addition to studying anatomic substrates of ventricular tachyarrhythmias in ischemic heart disease, pathologists have played a crucial role in analyzing the morbid anatomy of the non-ischemic cardiomyopathies and correlating specific features with risk of sudden death. In this general area, impactful papers have been published in *CVP* including the first description of the cardiac pathology in a recessive cardiocutaneous syndrome caused by a recessive truncation mutation in the desmosomal protein desmoplakin [30], analyses of anatomic substrates of sudden death in arrhythmogenic right ventricular cardiomyopathy [31,32], and arrhythmia substrates in heart failure [33]. There have also been instructive papers focused on the pathology of sudden death in young