The pathology of sudden cardiac death in patients with ischemic heart disease—arrhythmology for anatomic pathologists

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Abstract

The goal of this review is to help anatomic pathologists interpret the significance of pathologic changes in the hearts of patients with coronary artery disease who died suddenly of spontaneous ventricular arrhythmias. Attention is focused on dynamic interactions between triggering events, such as acute ischemia, and stable anatomic substrates of arrhythmias, such as healed myocardial infarcts. A basic knowledge of arrhythmia mechanisms is necessary to understand the role of pathologic anatomy in the pathophysiology of sudden death.

Keywords: Arrhythmia triggers; Arrhythmia substrates; Impulse conduction; Intercellular coupling; Current–load mismatch

1. Introduction

Pathologists are frequently asked to investigate and explain sudden deaths. Potential causes of sudden death are numerous, but the single most important cause by far is the spontaneous development of a lethal ventricular tachyarrhythmia in patients with ischemic heart disease [1,2]. There is usually no specific anatomic pathology of sudden cardiac death [3,4]. Pathologists must therefore know enough about the pathophysiology of sudden death to properly interpret the significance of the pathologic findings. The purpose of this review is to consider sudden cardiac death from the perspective of the anatomic pathologist. Attention is focused on basic mechanisms of lethal ventricular arrhythmias and the common pathologic findings in patients with ischemic heart disease who die suddenly. Selected aspects of the pathobiology of sudden death are discussed to help pathologists better understand the pertinent pathologic anatomy in the context of the pathophysiology of arrhythmogenesis.

2. Major causes of sudden cardiac death and identification of patients at risk

Prospective identification of individuals at risk for sudden death remains a major challenge [1,2]. Powerful predictors of sudden death have been defined in highly selected groups, such as patients who exhibit episodes of ventricular tachycardia and/or ventricular fibrillation during the convalescent phase of myocardial infarction, or those who survive out-of-hospital cardiac arrest [1,2]. But, as shown in Fig. 1, these high-risk subgroups make up only a small minority of total sudden deaths, which still number ~325,000/year in the United States. In fact, the majority of sudden deaths occur out-of-hospital in apparently healthy individuals who typically exhibit coronary artery disease at autopsy but who may have shown little clinical evidence of heart disease during life [1,2]. One compelling impetus to reduce the toll of out-of-hospital sudden deaths with automatic external defibrillators [5] and other strategies is the fact that survival after successful resuscitation from
sudden death is far greater in low-risk subgroups with no history of previous cardiovascular events than in high-risk patients whose cardiac arrests follow major cardiovascular events ([1]; Fig. 1).

As shown in Fig. 2, sudden cardiac death may occur in patients who exhibit structurally normal hearts at autopsy [3,4]. Some (perhaps many) of these patients have “channelopathies”, genetic diseases in which mutations in genes encoding sodium, potassium, and calcium channel proteins, for example, are responsible for sudden death syndromes such as the long QT syndrome [7,8], Brugada syndrome [9], and catecholaminergic polymorphic ventricular tachycardia [10]. Although fascinating and highly informative in terms of elucidating molecular mechanisms underlying some arrhythmias [11], these genetic sudden death syndromes are exceedingly rare, especially when compared with the prevalence of ischemic heart disease. Spontaneous lethal arrhythmias are also an important mechanism of death in patients with dilated [12] and hypertrophic [13] cardiomyopathies, primary diseases of cardiac myocytes that typically lead to marked changes in cardiac structure. However, most sudden deaths occur in patients with ischemic heart disease caused by coronary artery atherosclerosis [1,2]. Typically, these individuals have complex, localized anatomic substrates, such as discrete healed myocardial infarcts or left ventricular aneurysms or more diffuse structural alterations, such as variable degrees of cardiac myocyte hypertrophy and interstitial fibrosis. The most frequent clinical scenario in which sudden death occurs involves the development of acute ischemia (a transient triggering event) in an area of the heart containing a healed infarct (a common anatomic substrate).

The spontaneous development of a lethal cardiac arrhythmia may be regarded as a stochastic event that arises from complex interactions between relatively fixed
anatomic and functional substrates and transient triggering events [1]. As pathologists, we see and analyze anatomic substrates of arrhythmias, such as coronary artery atherosclerosis, ventricular hypertrophy and scarring, and other alterations of myocardial structure that increase the risk of spontaneous lethal arrhythmias in the setting of acute initiating events, such as acute ischemia, neurohormonal activation, changes in electrolytes, or other transient stresses. Recognizing and understanding the contributions of anatomic substrates to arrhythmogenesis is critical to the detailed pathologic analysis of sudden cardiac death, but this can only be accomplished by also understanding the complex, dynamic interactions between substrates and transient triggers.

3. The pathology of cardiac arrhythmias

Occasionally, a feature of the standard electrocardiogram can direct the pathologist’s attention to a particular site in the heart and lead to the discovery of specific anatomic findings, such as an accessory atrioventricular connection in Wolff-Parkinson-White syndrome or a lesion that disrupts a discrete component of the conduction system causing new bundle branch block. For example, Fig. 3 shows the heart of a patient with metastatic cervical carcinoma who developed right bundle branch block on the surface electrocardiogram shortly before death [14]. At autopsy, the moderator band, anterior papillary muscle of the tricuspid valve, and a circumscribed transmural region of the right ventricular free wall were extensively replaced by carcinoma. The metastatic tumor caused right bundle branch block by destroying Purkinje fibers within the moderator band, a structure that carries a major component of the right bundle responsible for conducting current from the basal ventricular septum to the right ventricular free wall.

Although gratifying, it is unusual to identify a definitive anatomic cause of an arrhythmia. Many pathologists automatically think that a detailed histological analysis of the cardiac conduction system is required to fully investigate cases of sudden cardiac death, but in reality, lethal arrhythmias usually arise as a result of pathologic changes affecting the working ventricular myocardium. Components of the conduction system can certainly participate in a ventricular tachyarrrhythmia circuit (e.g., bundle branch reentry tachycardia in nonischemic cardiomyopathies), but it is seldom rewarding to undertake a detailed pathologic analysis of the cardiac conduction system in most victims of lethal ventricular tachyarrhythmias, especially in the setting of ischemic heart disease.

Table 1 outlines the autopsy approach to the analysis of sudden cardiac death in patients with coronary artery disease. First, there must be thorough documentation of anatomic substrates of lethal ventricular arrhythmias in the myocardium, such as the degree of cardiac myocyte hypertrophy, the distribution of interstitial and/or replacement fibrosis, and the presence and distribution of acute cardiac myocyte necrosis. Second, critically related disease processes must be identified and quantified. The great majority of sudden death victims will have vulnerable coronary artery atherosclerotic plaques with or without thrombosis, but anatomic features of other common conditions which affect the myocardium, such as hypertension, valvular heart disease, and congenital heart disease, should be sought and characterized. Third, there must be a systematic search for other potential causes of sudden death, such as pulmonary thromboembolism or massive bleeding associated with disease processes in the aorta or cerebral arteries. As emphasized previously, the anatomic findings in sudden death are usually nonspecific, no matter how thorough the investigation. Therefore, the pathologist must have a basic working knowledge of arrhythmia mechanisms to understand properly the contributions of substrates in sudden death.

4. Mechanisms of cardiac arrhythmias

In general, cardiac arrhythmias arise as a result of disorders of electrical impulse formation and/or disorders of electrical impulse conduction. In most cases, abnormalities in both impulse formation and conduction probably contribute importantly to arrhythmogenesis.
Disorders of impulse formation may arise in the normal pacemaker (sinus node), resulting in sinus bradycardia (sick sinus syndrome) or sinus tachycardia. However, in the context of lethal ventricular arrhythmias, disorders of impulse formation usually develop in distal components of the conduction system or in working ventricular myocytes and result in aberrant, premature beats caused by abnormal automaticity or triggered activity. These events arise from the inherent ability of electrically active cells to spontaneously depolarize and generate an action potential.

Abnormal automaticity is defined as spontaneous initiation of an impulse that is independent on prior stimulation. This typically occurs under conditions of enhanced sympathetic and/or decreased parasympathetic tone, acidosis, hypoxia, and hypercapnea. Abnormal automaticity often develops in injured ventricular myocytes with reduced resting membrane potentials or in Purkinje fibers with reduced diastolic threshold potentials, electrophysiologic abnormalities that result from the complex homeostatic perturbations produced by acute ischemia. Triggered activity is the initiation of an impulse that arises consequent to a preceding impulse or series of impulses. Thus, triggered activity is manifest as early or late afterdepolarizations, inappropriate impulses that arise before or after the full repolarization of a cell or group of cells in which abnormal ionic conditions prevail. Fig. 4 illustrates an early afterdepolarization occurring in an injured cell. The afterdepolarization originates during the repolarization phase of the action potential before the cell has returned to a stable resting membrane potential. Conditions favoring the formation of early afterdepolarizations include hypoxia, acidosis, decreased intracellular K+, and increased intracellular Ca2+ concentrations, all of which are typically observed in the setting of acute ischemic injury.

Abnormal automaticity and triggered activity both have the potential to activate the heart at an ectopic site, before the next sinus beat activates the myocardium in the normal, coordinated temporal and spatial sequence. Depending on multiple factors such as the site in which the ectopic beat originates, the refractoriness of adjacent tissue, and potential structural alterations of the surrounding myocardium, the abnormal beat may give rise to a sustained arrhythmia either by reentry (see below) or a non-reentrant mechanism. In the latter case, the ectopic focus itself may continue to fire at a rapid rate and produce a tachyarrhythmia in which the myocardium is activated in an aberrant spatial pattern that compromises contractile function. This appears to be the mechanism in some types of paroxysmal atrial fibrillation in which bursts of ectopic activity arising in myocytes lining the pulmonary veins have been implicated [15]. It should be stressed, however, that there is no possible way, using the conventional tools of anatomic pathology, to identify cell(s) that exhibit abnormal automaticity or triggered activity. In most ventricular arrhythmias caused by abnormal automaticity or triggered activity, these electrical events probably arise in normal appearing cells with deranged ionic homeostasis caused by acute ischemic injury.

Disorders of impulse conduction play an important role in sudden death by promoting tachyarrhythmias dependent upon reentry. To understand reentry, it is important to understand the principal determinants of electric impulse propagated in cardiac muscle. Impulse propagation depends on (1) the amount of current generated by proximal impulse propagated in cardiac muscle. Impulse propagation depends on (1) the amount of current generated by proximal cells in the conduction pathway (determined principally by the density and activity of sodium channels), (2) the extent to which cardiac myocytes in the conduction pathway are electrically coupled by gap junctions (i.e., the resistance to current flow across cell borders), and (3) the excitability of the distal tissue into which the impulse is being propagated (i.e., how much current is required to activate downstream cells). Abnormal impulse conduction is an obligatory feature of reentry, a common arrhythmia mechanism producing lethal tachyarrhythmias such as ventricular tachycardia and fibrillation.

Reentry can be understood by first considering normal electrical activation. During the normal cardiac cycle, electrical activity generated in the sinus node is conducted throughout the myocardium until the entire heart has been activated. During the absolute refractory period, the impulse has “no place to go” and dies out. Myocytes recover excitability but normally remain quiescent until the next impulse begins in the sinus node. Reentry arises as a consequence of altered impulse conduction (Fig. 5). In this setting, a group of abnormal myocytes does not become activated during a normal wave of depolarization, either because conduction through it is blocked in one direction or because it had not recovered excitability when the impulse first arrived (i.e., it was still refractory to activation). In either case, the wavefront travels around this region, during which time the abnormal cells can recover excitability and become activated from another direction or through another conduction pathway. This late-activating region can then serve as an electrical link to reexcite (i.e., reenter) postrefractory areas that had recovered excitability from the initial depolarization (Fig. 5). Reentry has the primary prerequisite of unidirectional conduction block, which occurs in tissue with altered conduction properties or recovery of excitation. As a general rule, conditions that decrease conduction velocity and/or decrease refractoriness promote reentry, whereas

**Fig. 4. Intracellular action potential recordings showing a normal action potential (left) and an early afterdepolarization in an injured cell (right).**

**Early Afterdepolarization (EAD)**

Conditions favoring EAD formation:
- hypoxia, acidosis, ↓[K+], ↑[Ca2+]
conditions that enhance conduction velocity and/or prolong refractoriness diminish the development of reentry.

5. Dynamic interplay between arrhythmia mechanisms and anatomic substrates

It is clear from the foregoing discussion that alterations in active depolarizing and repolarizing currents are at the heart of arrhythmia mechanisms involving abnormalities of impulse formation (abnormal automaticity and triggered activity) and, to a certain extent, abnormalities of impulse propagation. Indeed, these electrical derangements can lead to lethal arrhythmias in structurally normal hearts (in the long QT syndrome or catecholaminergic polymorphic ventricular tachycardia, for example). In most cases, however, abnormalities in depolarizing and repolarizing ionic currents arise not from in-born errors but from transient triggering events (e.g., acute ischemia or neurohormonal activation) and interact with existing anatomic substrates to produce lethal arrhythmias. Although the pathologic anatomy of arrhythmia substrates is nonspecific and usually insufficient to cause an arrhythmia by itself, structural alterations in the diseased heart provide the “fertile soil” in which conduction disturbances inherent in the substrates may, in combination with transient electrical abnormalities, lead to reentrant arrhythmias.

The pathologic features of anatomic substrates of recurrent sustained ventricular tachycardias were elucidated during the development of modern clinical electrophysiology [16] when, for the first time, reentrant ventricular arrhythmia circuits were mapped in patients and discrete regions exhibiting conduction block and slowing were identified and shown to be necessary for the development of reentrant arrhythmias [17,18]. This led to surgical procedures to interrupt arrhythmia circuits by excising critical tissues, usually located in subendocardial areas near healed infarcts or surrounding ventricular aneurysms [19,20]. Pathologic analysis of the surgical excisions [21,22] revealed bundles of myocardial fibers embedded in dense fibrous tissue (Fig. 6). Although separated from one another by fibrous tissues, these bundles often extended uninterrupted to the margins of the resection specimen [21]. Myocytes within the bundles were viable but exhibited loss of sarcomeres and aggregates of dilated sarcoplasmic reticulum. Electrophysiologic studies demonstrated that conduction through these critical areas was highly discontinuous and heterogeneous [22,23]. Areas of conduction block were frequently encountered. It was subsequently
shown that the major defect responsible for the slow, haphazard conduction and conduction block was the remodeling of intercellular connections at gap junctions, a consequence of fibrosis and focal loss of cells, which significantly reduced the extent to which cells were connected to one another [22,24]. As described below, there is now a reasonably sophisticated understanding about how this type of structural remodeling can lead to unidirectional block, the critical ingredient of reentry.

6. Intercellular coupling, current–load, and conduction

How do the anatomic substrates typically found in sudden death victims lead to development of unidirectional conduction block and reentrant arrhythmias? This question has been the subject of computer modeling and experimental studies that incorporate fundamental features of human arrhythmia substrates. One particularly informative experimental system involves neonatal rat ventricular myocytes grown in vitro in patterned arrays, in which long, narrow strands of myocytes are connected to a larger mass of cells [25–27]. This pattern is a reasonable simulation of the pathologic anatomy of human ventricular arrhythmia substrates in which bundles of myocytes, separated from one another by fibrosis, eventually connect with structurally normal tissue at the edge of the remodeled region. Using optical mapping techniques to measure transmembrane voltage changes, it is possible to delineate the conduction properties of these tissue patterns in vitro with high resolution [25]. As shown in Fig. 7A, when an impulse is initiated in a strand and propagates in the direction of the mass, a marked slowing of conduction develops at the isthmus, the region where the slender strand expands into the mass [26]. Conduction slowing is evident by the crowding of isochrones (each showing a region of tissue activated within a given time interval) and by the flattening of action potential upstrokes in the isthmus (Fig. 7A). Conduction slowing at the expansion from strand to mass is a consequence of the current–load relationship in this tissue pattern. This fundamental rule of electrical impulse propagation is predicated on the fact that a certain amount of current must be generated to ensure that cells downstream will be activated. The amount of current required to maintain propagation is determined by the “load” on the cells producing the current, which, in turn, is determined by the number of cells that must be depolarized and the extent to which cells in the conduction pathway are electrically coupled to one another. When a cell depolarizes and generates an action potential, it produces current that flows

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**Fig. 7.** Impulse propagation in cultured rat ventricular myocytes grown in patterned arrays consisting of strands connected to large masses of cells. The locations of photodiode optical recording sites are indicated by circles. Optical action potentials are shown to the right of each photodiode recording site. (A) An impulse is initiated in the strand and travels toward the mass. As the activation wavefront approaches the isthmus, isochrones showing regions of tissue activated within 200-μs intervals become crowded, indicating that conduction velocity has slowed. Action potential upstrokes also become less steep, indicating that the rate of depolarization has diminished. These changes are caused by the increased load imposed by the large number of well-coupled cells in the cell mass. These cells siphon off current into the mass, thus reducing current available to depolarize cells in the isthmus. (B) In contrast, when activation is initiated in the mass and the wavefront travels into the strand, propagation across the isthmus is rapid. This experiment illustrates how geometric features alone can result in unidirectional conduction slowing due to different current–load relationships. Reprinted with permission from Ref. [26].
across cell junctions to activate the next cell in the pathway. However, some of this current also flows downstream to distal cells in the pathway, thus reducing the amount of current available to depolarize the cells and maintain active propagation. If the amount of current generated exceeds the load, then conduction is maintained, but if load exceeds current, then conduction is blocked. Returning to the experiment shown in Fig. 7, it is apparent that only a limited amount of current can be generated in the strand because of the small number of cells within the strand. This amount of current is sufficient to maintain propagation in the strand because the load is also low. However, as current begins to flow into the isthmus, the increased load imposed by the much greater number of well-coupled cells acts as a sink to dissipate some of the current. This increases the time required to bring cells at the isthmus to threshold and therefore results in slower conduction. With this explanation in mind, it is easy to understand how an impulse initiated within the mass generates more than enough current to rapidly cross the isthmus and activate cells in the strand ([26]; Fig. 7B).

The experiment in Fig. 7 illustrates how unidirectional conduction slowing can occur in normal cells that are normally coupled, based solely on current–load mismatch inherent in the structure of the system. It is not difficult to imagine what would happen if the amount of current produced in a thin strand were insufficient to activate the large mass of cells to which it was attached ([27]; see Fig. 8). The obvious result would be unidirectional conduction block, the key pathogenic feature of reentry. It is plausible to suggest that strands and masses of cells in vitro are a reasonable approximation of what occurs in the hearts of patients with healed infarcts. As demonstrated by the pathologic analysis of resection specimens from patients with recurrent ventricular tachycardia [21,22], critical regions in the arrhythmia circuit are typically composed of discrete bundles of viable cells that eventually connect with areas of structurally normal myocardium. It seems likely, therefore, that structural alterations leading to current–load mismatch play a critical role in reentrant arrhythmias in patients with ischemic heart disease.

7. Remodeling of intercellular connections and the pathogenesis of sudden death

In the normal ventricle, myocytes are extensively connected to many neighbors in varying degrees of end-to-end and side-to-side apposition. Three-dimensional reconstructions have revealed that, on average, a single ventricular myocyte is connected to ~11 neighbors ([28,29]; Fig. 9). Roughly half of these neighbors are connected to an individual cell in a purely or predominantly side-to-side orientation (shown as Type I and II connections in Fig. 9), while the remaining connections are oriented in end-to-end fashion (Type III and IV connections). This pattern of intercellular connections ensures that activation wavefronts moving through a uniform sheet of ventricular myocardium
can propagate efficiently in both longitudinal and transverse directions (i.e., parallel and perpendicular to the long fiber axis, respectively).

The high degree of intercellular connectivity created by numerous large gap junctions makes it appear that conduction through normal ventricular myocardium is a continuous process, as though impulses were propagating through a uniform conductive medium. The fact remains, however, that myocardium is composed of individual cells, and impulse propagation depends on current flow from one discrete cell to another. It follows, therefore, that structural remodeling of myocardium leading to a reduction in the extent to which myocytes are connected to one another will make conduction more discontinuous. As the resistance to current flux across cell borders increases, macroscopic patterns of conduction become complex and haphazard, especially if the tissue has been “broken up” by spatially heterogeneous patterns of myocyte loss and fibrosis [22,30]. Morphometric reconstructions have shown that myocytes in regions bordering healed infarcts are connected by fewer and smaller gap junctions [28]. The average number of interconnections in border zones is reduced by nearly half, due primarily to loss of lateral connections [28]. For example, the number of infarct border zone myocytes connected in side-to-side configuration is reduced by 75%, whereas connections end-to-end are reduced by <25% ([28]; Fig. 9). When these regions are activated by wavefronts traveling in a direction parallel to the cells long axis, propagation is relatively rapid because end-to-end connections are largely preserved. If, however, a wavefront initiated by an ectopic beat activates this region in a direction perpendicular to the long cell axis, conduction will be slow, discontinuous, and liable to block because side-to-side connections are selectively disrupted and impulses are forced to zigzag through the tissue [30]. The complex pathways followed by such wavefronts undoubtedly produce the fractionated electrograms and late potentials that are characteristic of border zone regions [22]. And finally, if a transient episode of acute ischemia is superimposed on this substrate, the tendency toward altered impulse formation (abnormal automaticity or triggered activity), combined with the preexisting altered conduction properties and the current–load relationship in the anatomic substrate, creates conditions that, at least on a statistical basis, are highly conducive to reentrant arrhythmias.

8. Conclusion

Anatomic substrates of ventricular arrhythmias are common. Substrates that may potentially give rise to lethal arrhythmias occur in many more people than those who ultimately succumb to fatal arrhythmias. Clearly, much more is involved in arrhythmogenesis than the presence of an infarct scar or a region of interstitial fibrosis. There is no easy way for the pathologist to elucidate triggers and document their pathophysiologic importance using conventional methods of anatomic pathology. The intelligent analysis of the pathology of sudden death therefore requires an understanding of the pathology of arrhythmia substrates and the pathophysiologic mechanisms that make them dangerous.

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