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Ischemic Ventricular Arrhythmias Experimental Models and Their Clinical Relevance

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Abstract

In the United States, sudden cardiac death accounts for an estimated 300,000 to 350,000 cases each year, 80,000 presenting as the first manifestation of a preexisting, sometimes unrecognized, coronary artery disease. Acute-myocardial infarction (AMI)-induced ventricular fibrillation (VF) frequently occurs without warning, often leading to death within minutes in patients who do not receive prompt medical attention.

Identification of patients at risk of AMI-induced lethal ventricular arrhythmias remains an unmet medical need. Recent studies suggest that a genetic predisposition may significantly contribute to the vulnerability of the ischemic myocardium to ventricular tachycardia (VT)/VF.

Numerous experimental models have been developed for the purpose of advancing our understanding of the mechanisms responsible for the development of cardiac arrhythmias in the setting of ischemia and with the aim of identifying antiarrhythmic therapies that could be of clinically benefit. While our understanding of the mechanisms underlying AMI-induced ventricular arrhythmias is coming into better focus, risk stratification of patients with AMI remains a major challenge.

This review briefly discusses our current state of knowledge regarding the mechanisms of ischemic ventricular arrhythmias and their temporal distribution as revealed by available experimental models, how these correlate with the clinical syndromes, as well as prospective prophylactic therapies for the prevention and treatment of ischemia-induced life-threatening arrhythmias.

Keywords

Acute Myocardial Infarction; Ischemia; Ventricular Fibrillation; Sudden Cardiac Death; Electrophysiology

1. Introduction

Lethal ventricular arrhythmias, including sustained ventricular tachycardia (VT) and, in particular, ventricular fibrillation (VF), are the immediate cause of cardiac arrest in the majority of the estimated 300,000 to 350,000 cases of sudden cardiac death (SCD) that

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occur annually in the United States of America (USA).^{1–3} SCD comprises 13% of all natural causes when defined as that occurring within one hour from the onset of symptoms.⁴ A major cause of SCD in the USA is acute myocardial infarction (AMI; ~250,000 cases per year) during both the reversible phase (ischemic phase) as well as during the infarct evolution phase. Cardiac arrest secondary to AMI induced-VF occurs commonly without warning. Because spontaneous conversion of VF to non-lethal rhythms is rare, out-of-hospital VF progresses to death within minutes in more than 95% of the victims. AMI induced-VF leads to SCD as the first manifestation of a preexisting coronary artery disease in about 80,000 people per year.^{1–3}

Experimental studies indicate that ischemia- or infarction-induced heterogeneities in excitability, refractoriness and/or conduction create the substrate and that ectopic excitation by a variety of mechanisms may provide the extrasystoles that trigger lethal ventricular arrhythmias.^{5–12}

2. Mechanisms of Ischemic Ventricular Arrhythmias (IVA)

Following total occlusion of a coronary artery, ventricular arrhythmias (Phase 1 [A and B] and Phase 2; see below) develop as a consequence of focal as well as non-focal mechanisms, the former due to automatic and non-automatic ectopic excitation and the latter involving reentry (Figure 1). *Automatic focal excitation* in depolarized ventricular myocytes may be the consequence of depolarization-induced automaticity (or abnormal automaticity; AA). It may also result from early (EADs) and/or delayed (DADs) afterdepolarization-induced triggered activity following Ca^{2+} overload (see section 4). *Non-automatic focal activity* includes responses arising as a consequence of currents of injury (systolic and diastolic), reflection and/or phase 2-reentry.^{2, 7, 13} In contrast, the *non-focal sources* of ischemia-mediated ventricular arrhythmias involve classical reentry, resulting from disordered conduction of the cardiac impulse such that instead of dying out after complete activation of the ventricular myocardium, the impulse persists to re-excite it. Reentry can manifest as VT and/or VF. Pre-requisites for reentry include unidirectional block and slow conduction of the cardiac impulse effecting re-excitation. Nonetheless, in regionally ischemic myocardium, ectopic excitation triggered by either abnormal automaticity, EADs, DADs, currents of injury, reflection, phase 2-reentry or reentry, can give rise to VT/VF.

3. Temporal Distribution of Ischemia-mediated Ventricular Arrhythmias (IVA)

Two temporally distinct phases of ventricular arrhythmia develop in response to ischemic injury. Phase 1 is the reversible phase of AMI, whereas Phase 2 is the infarct evolution phase (Figure 1). Phase 1, occurring during the first 2 to 30 minutes, is divided in 2 sub-phases called Phase 1A (2–10 min) and Phase 1B (15–30 min). The bimodal nature of Phase 1, however, is not universal among species. For instance, two peaks of early IVA can be readily observed in canine and pig models, but only one peak at ~15–20 min of ischemia is seen in rats and rabbits (Figure 2).^{1, 14} It is estimated that approximately 50% of SCD occurring after an AMI in humans takes place during the reversible phase (Phase 1) of ischemic injury.

In the vast majority of cases, Phase 1A arrhythmias appear to arise from reentry and manifest as bursts of VTs that rarely evolve into VF. Studies involving *in vivo* mapping of activation with high spatial resolution recording systems substantiate the initial observation of continuous and fragmented (multiple deflections) local electrograms suggestive of reentry. In contrast, Phase 1B arrhythmias may emerge from both focal as well as non-focal sources and are associated with less electrogram fragmentation. Indeed, abnormal

automaticity as well as reentry may take place during Phase 1B; the former as a result of release of endogenous catecholamines (known to occur at 15–20 min of ischemia) and the latter secondary to cell-to-cell electrical uncoupling giving rise to delayed conduction. In addition, the mechanical stretch induced by the viable myocardium that surrounds the ischemic zone may also account for the development of premature ventricular contractions (PVC) leading to IVA during Phase 1B; these PVCs typically arise from the border zone. Other arrhythmia mechanisms thought to generate PVCs at the border zone are currents of injury and phase 2-reentry.¹³ Phase 1B IVA more frequently evolve into VF (in contrast to Phase 1A) and are associated with accentuation of Ca^{2+} loading¹⁵ and a resultant increase in longitudinal resistance.¹⁶

If the acute bimodal phase of IVA (Phases 1A and 1B) is not fatal and reperfusion is not attained at the time the myocardial damage is still reversible (first 20–30 min following ligation), an infarct starts to evolve (Phase 2). Phase 2 IVA¹⁷ can be identified beginning at approximately 1.5 to 5 hours after the onset of the experimental AMI and lasts 2 to 3 days (Figure 1). Similar mechanisms as those described for Phase 1B appear to underlie the arrhythmias occurring during Phase 2 (infarct evolution phase) including focal and non-focal sources. Abnormal automaticity in surviving Purkinje fibers^{18, 19} are among the distinct arrhythmogenic foci proposed to underlie IVA during this phase.^{2, 17} Phase 2 IVA are believed to be associated with reperfusion of ischemic areas.²

Although the timing of human IVA is not well characterized, a similar sequential vulnerability to VF is observed, as in the experimental models. These data are consistent with experimental phases 1 and 2, associated with a reversible phase and an infarct evolution phase, respectively.¹⁷ It is noteworthy that approximately half of patients resuscitated from VF do not exhibit verifiable infarction.¹⁷

4. Biochemical and Electrophysiological characteristics of Phase 1 and Phase 2 Ischemia-related Ventricular Arrhythmias

Depletion of intracellular adenosine ATP combined with buildup of ADP and accumulation of products of anaerobic glycolysis, including lactic acid and ATP-derived hydrogen ions, which cause a fall in intracellular pH, underlie the metabolic dysfunction that occurs during the reversible phase of an AMI (Phase 1 IVA, first 30 min). This phase is also associated with interstitial accumulation of K^+ , catecholamines and amphiphiles such as lysophosphatidylcholine (a phospholipid that accumulates in ischemic myocardium), which significantly alter electrophysiologic properties, thus contributing to arrhythmogenesis.²⁰

Intracellular acidification activates the Na^+/H^+ exchanger resulting in H^+ extrusion in exchange for Na^+ entry (which leads to elevated intracellular Na^+). This in turn results in cell swelling and Ca^{2+} overload, the latter secondary to activation of the $\text{Na}^+/\text{Ca}^{++}$ exchanger operating in the reverse mode (Na^+ is extruded in exchange for Ca^{++}). These metabolic changes are accompanied by electrophysiological derangements, including membrane depolarization (mainly due to accumulation of K^+ in the extracellular space) causing Na^+ channel inactivation and reduced fast Na^+ current, leading to slowed conduction and altered refractoriness. In addition, an increase in the late sodium current (late I_{Na}) has been recently suggested to contribute to elevating intracellular Na^+ and thus to be responsible for the initial prolongation of the action potential duration (APD). Ultimately, the abbreviation of the APD observed during ischemia is the consequence of both decreased inward currents, including inward calcium current (I_{Ca}) (inhibited by the acidosis) and enhanced outward currents, including $\text{I}_{\text{K-ATP}}$ (ATP-sensitive potassium current); activated by the reduction in intracellular ATP following hypoxia, the latter playing the more prominent role.^{21, 22}

The infarct evolution phase (Phase 2 IVA), in which a nearly complete cessation of anaerobic glycolysis occurs, is distinguished by low glycogen and high lactic acid intracellular content, reduction of ATP levels to $\leq 10\%$ of normal, Na^+ and Ca^{++} overload, and further extracellular K^+ accumulation that at this stage may exceed 20 mM. Surviving Purkinje fibers exhibiting abbreviated action potentials of reduced amplitude, as well as depolarized membrane potentials and reduced V_{max} , have been proposed to be the main arrhythmogenic foci during this infarct evolution period.¹⁷

Nevertheless, rather than a single source or triggering event, it is likely that what ultimately underlies the susceptibility to SCD during an AMI is the interaction among many of the biochemical and electrophysiological disturbances implicated, acting in concert with a number of genetic predispositions yet to be identified.²³

5. Experimental Models of IVA

A variety of experimental models have been developed to examine the electrophysiologic disturbances associated with AMI. Isolated ventricular myocytes are used to study the electrophysiologic effects of “simulated” ischemia on action potentials, membrane currents and exchangers by exposing cells to metabolic inhibitors as well as hypoxic, acidic and hyperkalemic solutions. However, *in vivo* or *in vitro* studies using experimental models undergoing “regional ischemia” have proved to be ideal for studying AMI-induced VF.^{7, 10, 12, 13, 17, 20, 24–28} In fact, these models have provided the majority of the data on IVA and their suppression by drugs.¹⁷

In a mouse Langendorff model of regional ischemia (left coronary artery [LCA] occlusion)-induced *spontaneous* VF recently developed by Stables and Curtis,²⁷ the coronary perfusate consisted of a modified-Krebs solution containing low K^+ (3 mM), high Ca^{++} (2.4 mM) and catecholamines (epinephrine [313 nmol/L] plus norepinephrine [75 nmol/L]) in an effort to mimic the *in vivo* environment. In this model, the incidence of regional ischemia-induced *spontaneous* VF increased gradually during the first 30 min of LCA occlusion (Figure 4) in contrast to the absence of VF in hearts undergoing regional ischemia while perfused with the classic Krebs solution (which typically is devoid of catecholamines). These data suggest that the autonomic nervous system plays a central role in the pathogenesis of AMI-induced VF. In this respect, it was shown that following an AMI, chronic beta blockade improves survival (reduces the incidence of SCD), particularly in patients with left ventricular dysfunction in which the activity of the sympathetic nervous system is known to be significantly increased.²³

As stated earlier (see section 4), intracellular acidification is followed by an increase in intracellular Na^+ , which in turn leads to calcium overload by means of $\text{Na}^+/\text{Ca}^{++}$ exchanger operating in reverse mode. Calcium overload, in turn, is followed by electrophysiological derangements (EADs and DADs) that are implicated in ischemia-induced arrhythmogenesis. The cardiac protection provided by $\text{Na}^+/\text{Ca}^{++}$ exchange inhibitors in experimental models, including KBR-7943, SEA-0400 and amiloride^{29, 30} is therefore accredited, at least in part (since they are non-selective inhibitors), with prevention of calcium overload, making inhibition of this exchanger a hopeful target for cardiac protection. It is noteworthy that in a mouse model of global ischemia, hearts lacking $\text{Na}^+/\text{Ca}^{++}$ exchanger (NCX-knockout mice) had significantly less ischemia/reperfusion injury than hearts of wild type mice.¹⁰ Also, the use of Na^+/H^+ exchange inhibitors has been shown to reduce myocardial injury by its action to attenuate calcium overload during ischemia, thereby reducing ischemia and reperfusion injury. These studies strongly link calcium overload with the genesis of arrhythmias and irreversible myocardial damage.¹⁰

More recently, inhibition of the late I_{Na} current using ranolazine has been demonstrated to be antiarrhythmic in an *in vivo* rat model of regional ischemia (20 min of LCA occlusion) mimicking Prinzmetal's angina.³¹ Ranolazine reduced the frequency and duration of VT as well as incidence and duration of VF, and decreased mortality in a dose-dependent manner at therapeutic concentrations (2, 4 and 8 μ M). Late I_{Na} is believed to increase, particularly upon reperfusion, secondary to the formation of oxygen derived free radicals following the sudden availability of oxygen. Late I_{Na} is known to contribute to the increase in intracellular sodium, which in turn leads to calcium overload. Calcium overload, in addition to impairing left ventricular function (relaxation), causes afterdepolarizations. Thus, by its action to inhibit late I_{Na} , ranolazine would be expected to prevent the occurrence of DADs and EADs³² and thereby exert antiarrhythmic effects. Another recent study demonstrated a potent antifibrillatory effect of ranolazine following severe coronary stenosis in the intact porcine model.³³ This action appears to be due primarily to block of late I_{Na} and to be independent of coronary flow changes.

During Phase 1A of IVA (first 2–10 min), the large transient outward current (I_{to}) in ventricular epicardium (Epi), which is more prominent in the right ventricle, has been implicated in the genesis of ST segment elevation and VT/VF via the mechanism of phase 2 reentry. In a canine model of regional ischemia performed in the isolated arterially-perfused right ventricular (RV) wedge preparation, Yan et al.¹³ have demonstrated that loss of the RV Epi action potentials (AP) dome in the ischemic region can lead to a closely coupled extrasystole through phase 2-reentry. Phase 2-reentry occurred “across the border zone” secondary to propagation of the dome from the normal zone (where it is normally present) to the ischemic region (where it is lost after interruption of coronary flow). The extrasystoles generated in this manner were in turn capable of initiating VF (Figure 5). Based on this evidence, it is tempting to speculate that I_{to} blockers may also exert antiarrhythmic properties in the setting of early AMI, particularly if the RV is involved.³⁴ Obviously, the loss of the Epi dome would further reduce AP duration in the ischemic region (which is linked largely to reduced I_{Ca} and I_{K-ATP} activation) and may contribute to elevation of the ST segment.

A clinically relevant *in vivo* canine model of acute ischemia was recently developed by Issa et al.²⁴ The model is based on the induction of acute myocardial ischemia following occlusion of the left coronary circumflex. VT/VF develops in 72% of the animals in the setting of an anterior healed AMI induced by prior occlusion of the left anterior descending coronary artery with polyvinyl foam particles and induction of heart failure by rapid ventricular pacing.²⁴ This canine model offers a useful tool for studying ventricular arrhythmias under conditions similar to the clinical setting in which multiple substrates arising from a healed infarction, heart failure and increased sympathetic tone interact with acute myocardial ischemia. The model offers the possibility, like many others, of evaluating novel prophylactic antiarrhythmic strategies.

Identification of patients at risk of AMI-induced lethal ventricular arrhythmias remains a clinical challenge. A highlight of the problem is the notion that genetic variations (mutations and polymorphisms) may significantly contribute to the vulnerability of the ischemic myocardium to VT/VF.²³ Indeed, we have recently described the first loss of function-sodium channel mutation in the *SCN5A* gene that was associated with the development of VT/VF within the first 12 hours following an AMI.³⁵ Recent studies have also identified a common polymorphism of *KCNH2* (K897T) as being associated with an 8-fold increased risk for the development of post-MI QT prolongation and Torsade de Pointes (TdP) arrhythmias.^{35, 36} Whereas the hyperacute phase of ischemia and evolving infarction are associated with abbreviation of the AP, the healing phase of an MI is associated with a

prolongation of the action potential and QT interval, leading to TdP in those rare cases in which a genetic predisposition exists

Implantable cardiac defibrillators have become the standard protective measure in patients that have survived VT/VF since, at the present time, they can more effectively prevent SCD when compared with drugs. Indeed, although chronic beta blockade improves survival following an AMI (i.e. reduces the incidence of SCD), the use of classic antiarrhythmic drugs including flecainide, d-sotalol and amiodarone that typically block ion channels has been associated with adverse effects, including increased mortality.²³

6. Conclusion

While our understanding of the mechanisms underlying AMI-induced ventricular arrhythmias is coming into better focus, risk stratification of patients with AMI remains a major challenge. A number of well established experimental models and some recently developed models suggest that prevention of AMI-induced life-threatening ventricular arrhythmias is an achievable goal. Identification of the genetic predisposition to the development of arrhythmogenesis post-MI is another major goal for future research.

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Abbreviations

AA	Abnormal automaticity
AMI	acute myocardial infarction
AP	action potential
APD	action potential duration
DAD	delayed afterdepolarization
EAD	early afterdepolarization
Epi	epicardium
I_{Ca}	inward calcium current ()
IVA	ischemia-mediated ventricular arrhythmias
I_{to}	transient outward current
late I_{Na}	late sodium channel current
LAD	left anterior descending coronary artery
LCA	left coronary artery
PVC	premature ventricular contraction
RV	right ventricular
SCD	sudden cardiac death
TdP	torsade de Pointes
VF	ventricular fibrillation
VT	ventricular tachycardia

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Figure 1.

Temporal distribution and genesis of ischemic ventricular arrhythmias. VT: ventricular tachycardia; VF: ventricular fibrillation; AA: abnormal automaticity; EADs: Early afterdepolarizations; DADs: Delay afterdepolarizations (DADs); P2R: phase 2-reentry; PFs: Purkinje fibers.

Figure 2.

Incidence of ischemic ventricular arrhythmias and species-differences in their temporal distribution. A: Phase 1A and 1B in regionally ischemic anesthetized open-chest *pig hearts* (dashed area). Black line denotes percentage of animals with ventricular fibrillation (VF). The open circles indicate average rise in tissue impedance in all animals. The black line indicates the time course and number of animals with VF. Reproduced from reference¹, with permission. B: Time course of onset of VF in anesthetized *rats* (left) and *rabbits* (right) subjected to left coronary artery occlusion in which only one peak of early VF can be readily observed (Phase 1). Modified from reference,¹⁴ with permission.

Figure 3. Biochemical and electrophysiological characteristics of Phase 1 and Phase 2 ischemia-mediated ventricular arrhythmias. I_{Na}: sodium channel current; Late I_{Na}: late I_{Na}; APD: action potential duration; I_{Ca}: inward calcium current; I_{K-ATP}: ATP-sensitive potassium current

Figure 4.

Ischemia-induced ventricular fibrillation (VF) is increased by catecholamines. Analysis of VF observed during 30 min regional ischemia in isolated mouse hearts perfused with Krebs containing catecholamines or vehicle control and paced at 600 b.p.m. (A) Incidence of VF. (B) Incidence of VF over time. Modified from reference,²⁷ with permission.

Figure 5.

Acute regional myocardial ischemia resulting in complete loss of action potential dome at epicardium (Epi)2 within the ischemic zone, but not at Epi1 (recorded from the perfused side of the ischemic border), leading to propagation of the dome at Epi1 to Epi2 (phase 2 reentry) and initiating ventricular tachycardia/ventricular fibrillation. Modified from reference,¹³ with permission.