Ischemia, metabolic disturbances, and arrhythmogenesis: Mechanisms and management

Karthik Ramaswamy, MD; Mohamed H. Hamdan, MD

The development of ventricular arrhythmias is often a consequence of the interaction between structural abnormalities of the heart and transient disturbances in the electrophysiologic milieu. The critically ill patient is particularly susceptible to arrhythmias given the metabolic, ischemic, and neurohormonal stressors present in the intensive care unit. The significance of ventricular arrhythmias in the acute care setting is related to the presence of reversible causes and the extent of underlying heart disease. Long-term management of these patients is guided by an assessment of the risk for recurrent arrhythmias and the degree of left ventricular systolic dysfunction. In the absence of a reversible cause, symptomatic sustained arrhythmias are usually treated with an implantable cardioverter-defibrillator, a therapy that improves survival in this patient population. In many cases, however, proper long-term management of patients with ventricular arrhythmias is less clear, and the approach must be guided by a thorough understanding of the pathophysiology and the fundamental mechanisms of arrhythmogenesis. (Crit Care Med 2000; 28[Suppl.]:N151–N157)

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MECHANISMS OF ARRHYTHMOGENESIS

Cardiac arrhythmias arise as a result of abnormal impulse initiation or conduction. For better understanding of the fundamental mechanisms of arrhythmia formation, a brief review of the ionic currents underlying the genesis of the cardiac action potential is warranted.

The cardiac action potential represents the rapid flux of ions across the cell membrane of excitable tissue. The resultant depolarization travels across the heart and produces a wavefront of excitation. Figure 1 summarizes the ionic currents involved in the genesis of the cardiac action potential. At baseline, a resting potential of -80 to -90 mV is maintained as a result of a high level of potassium channel conductance. Phase 0 is the result of activation of fast sodium channels, phase 1 results from the transient outward potassium current, phase 2 (the plateau) results from a balance of inward (sodium and calcium) and outward (potassium) currents, and phase 3 (repolarization) results mainly from the delayed activation of potassium channels. In some cells, such as in the sinoatrial node and the atrioventricular node, repolarization is followed by spontaneous, gradual depolarization (phase 4) leading to another action potential. This process is called normal automaticity.

Independent of the relative importance of the pathologic substrate vs. the altered milieu, three fundamental electrophysiologic mechanisms are responsible for arrhythmia formation. These are reentry, abnormal automaticity, and triggered activity.

Reentry is the most common mechanism of arrhythmia formation. It results when a wavefront of excitation propagates in one direction while blocking in an adjacent direction, subsequently returns to the blocked area, and successfully excites this region leading to continuous electrical activation rather than being extinguished. The following three conditions are typically necessary for reentry to occur: the presence of a substrate in which a central area of excitable tissue separates two pathways for conduction; unidirectional block in one of the two pathways; and slow conduction permitting delay and recovery of excitability in the previously blocked area. These conditions may be anatomically defined, as in the tissue surrounding an infarct zone, or may be the result of functional alterations in conduction secondary to electrolyte disturbances or ischemia. Thus, patients in whom some, but not all, of the criteria necessary for reentrant arrhythmias are present may not develop any arrhythmias until exposed to factors producing...
changes in refractoriness or conduction.
Abnormal automaticity refers to the development of spontaneous, phase 4 depolarization and impulse formation in cells that otherwise do not exhibit automatic pacemaker activity. Normally contracting ventricular myocytes typically do not have spontaneous pacemaker activity, but under certain conditions these cells may develop a “leakage current” during phase 4, resulting in impulse formation. Ischemia can lead to this phenomenon (1), and diseased cardiac tissue is particularly susceptible to developing abnormal pacemaker activity. Abnormal automaticity, distinguished from normal automaticity, causes repetitive depolarization at rates faster than that found in normally automatic tissues, resulting in overdrive suppression of the sinoatrial node (2). Automatic cells in the atrioventricular node or His-Purkinje system may also usurp the sinus node pacemaker activity by a process called enhanced automaticity, in which phase 4 depolarization becomes accelerated by drugs, sympathetic activity, or metabolic disturbances.

Triggered activity refers to abnormal impulse formation from afterdepolarizations. Afterdepolarizations, which can be either early or delayed, are oscillations of membrane potential occurring during or immediately after repolarization (Fig. 1). Early afterdepolarizations are important in the genesis of torsades de pointes. The mechanism of early afterdepolarizations appears to be related to delayed reactivation of ion channels that carry inward depolarizing currents. These channels are responsible for the plateau phase of the action potential and normally become inactive during early repolarization (phase 3). When the action potential duration is prolonged, these channels may reopen, resulting in a net inward flow of ions. The result is positive oscillations called early afterdepolarizations. If early afterdepolarizations are of sufficient amplitude to reach threshold, abnormal impulse propagation is triggered. Therefore, the presence of early afterdepolarizations is favored by conditions that prolong action potential duration (a prolonged QT interval on the electrocardiogram), such as slow heart rates (action potential duration is inversely related to heart rate), antiarrhythmic drugs (quinidine, procainamide, and sotalol), and electrolyte disturbances, such as hypokalemia, hypocalcemia, and hypomagnesemia. On the other hand, delayed afterdepolarizations result from increased intracellular calcium levels. Thus, conditions that lead to arrhythmia formation from delayed afterdepolarization-induced triggered activity are generally associated with an increase in intracellular calcium. The classic example is digitalis intoxication. Digitalis inhibits the Na⁺/K⁺ pump resulting in increased intracellular Na⁺ that, in turn, results in increased levels of Ca²⁺ via the Na⁺/Ca²⁺ exchanger. Other causes of delayed afterdepolarizations and triggered arrhythmias are catecholamines and increases in heart rate (2). Ischemia also results in intracellular calcium overload and has been implicated as a cause of triggered arrhythmias (3).

EFFECTS OF METABOLIC DISTURBANCES AND ISCHEMIA ON ARRHYTHMOGENESIS

Metabolic disturbances and ischemia are common findings in the critically ill patient. Their influences on arrhythmogenesis are complex and not necessarily predicted by Nernst-Goldman equilibrium or by experimental findings from in vitro preparations. This is a result of concomitant alterations in ion channel conductance, effects on membrane ion exchangers, and synergistic or opposing effects of more than one abnormality. Nonetheless, a brief review of the electrophysiologic effects of these disorders helps the clinician appreciate the importance of these potentially modifiable factors in the ICU.

Metabolic Disturbances

The clinical features of rhythm disorders associated with specific electrolyte abnormalities are well known to most readers. Therefore, we will limit our discussion to the electrophysiologic basis underlying arrhythmogenesis during changes in potassium, calcium, and magnesium levels.

Potassium. Hypokalemia, as predicted by the Nernst equation, hyperpolarizes the resting membrane potential to more negative values, and consequently may cause slowing of conduction (4, 5). In addition, hypokalemia decreases potassium conductance and may enhance automaticity (4–7). However, the most important effect of hypokalemia is a delay in repolarization and prolongation of the action potential duration which may lead to early afterdepolarization formation and triggered arrhythmias. Hyperkalemia, on the other hand, has two major effects. First, it increases the permeability to potassium (5, 8), and second, it shifts the cell membrane resting potential to a less negative value. The result is shortening of the action potential duration, suppression of automaticity, and slowing of conduction. (4, 5, 9). At extremes of hyperkalemia, marked QRS widening (sine wave) is observed. Severe hyperkalemia requires prompt correction because its cardiac effects may be lethal. In the management of critically ill patients, it is our opinion that maintenance of high normal values of K⁺ is reasonable in view of its effects on action potential duration shortening, the prevention of early afterdepolarizations, and suppression of enhanced automaticity.

Calcium and Magnesium. Hypocalcemia causes QTc prolongation and thus, may result in early afterdepolarizations and triggered arrhythmias. Prolongation of the QTc secondary to acute hypocalcemia is a potential cause of torsades de pointes (10), although much less commonly than with hypokalemia or hypomagnesemia (11). On the other hand, hypercalcemia causes QTc shortening. Although excess intracellular calcium caused by digitalis toxicity, catecholamines, or ischemia can cause delayed afterdepolarizations and triggered arrhythmias, increased extracellular calcium concentration does not result in triggered arrhythmias (4, 12). Hypomagnesemia, although rarely an isolated disorder, is also associated with prolongation of the QTc interval and torsades de pointes. Hypermagnesemia, on the other hand, is not usually associated with clinical arrhythmias, although slowing of the AV node and ventricular conduction may be seen (4). Calcium and magnesium are important primarily for their interaction.
with other ions. Calcium is used to treat life-threatening hyperkalemia, and its effect is thought to be because of the resting membrane potential shifting to more negative values (5). Similarly, Mg²⁺ is used to treat torsades de pointes primarily by shortening action potential duration and suppressing early afterdepolarizations (13). It should also be noted that magnesium and potassium deficits often coexist making Mg²⁺ repletion particularly important in the management of hypokalemia.

Ischemia

Myocardial ischemia occurring in the ICU, either from underlying coronary artery disease or from hemodynamic and hypoxic stress, can produce a multitude of electrophysiologic effects. These include partial depolarization of the resting membrane potential resulting in inactivation of the fast sodium channels and slowing of conduction, increased intracellular calcium, elevation of extracellular potassium, and prolongation of refractoriness despite shortening of the action potential duration (14). The resulting effects on arrhythmogenesis are complex. Abnormal automaticity, triggered activity, and reentry can all result from these perturbations.

Miscellaneous

In addition to electrolyte shifts and ischemia, other systemic influences found in the critically ill patient, such as acid-base abnormalities, hypoxia, and enhanced catecholamine levels can also predispose to ventricular arrhythmias (14). The role of the sympathetic nervous system in arrhythmogenesis cannot be overemphasized. Through stimulation of the β-adrenergic receptor, sympathetic activation or exogenous catecholamines can result in enhanced automaticity or triggered activity. Reentry may also be facilitated, particularly in the presence of ischemia.

APPROACH TO VENTRICULAR ARRHYTHMIAS IN THE CRITICALLY ILL PATIENT

A few general principles regarding the evaluation of ventricular arrhythmias in the ICU deserve mention. Newly observed arrhythmias warrant an assessment of electrolytes, acid-base and oxygenation status, and a 12-lead electrocardiogram with particular attention to the QTc interval. The position of intravascular catheters should be evaluated, because occasionally, dislodgement can result in mechanically-induced arrhythmias. Prolongation of the QTc interval should prompt a search for potential causes, if not already apparent. Specific attention should be given to the morphologic characteristics of the tachycardia, and it should be emphasized that polymorphic ventricular tachycardia can be mistakenly labeled as monomorphic when observed in a few leads only. Routine assessment of cardiac enzymes is not mandatory with the onset of every arrhythmia, but should be guided by the clinical setting and the type of arrhythmia. For example, polymorphic ventricular tachycardia in the setting of a normal QTc interval is often the result of ischemia, whereas monomorphic ventricular tachycardia usually results from a fixed substrate (a scar) and rarely mandates a search for acute ischemia.

Another general problem commonly encountered in the ICU setting is the management of inotropic and vasoactive support in patients with ventricular arrhythmias. As previously discussed, catecholamines are an important component in the development of many arrhythmias, and consequently, a reduction or elimination of this factor is often helpful in the treatment of ventricular arrhythmias. On the other hand, arrhythmias resulting from decompensated heart failure may indeed subside with appropriately tailored hemodynamic therapy. Quite often, optimization of the hemodynamic status takes priority, and antiarrhythmic drug therapy may be required to treat symptomatic ventricular arrhythmias in the setting of continued inotropic and vasoactive support.

In the following section, we will discuss both acute and long-term evaluation and management of patients with ventricular arrhythmias. In the first part, we will discuss the approach to ventricular ectopy and monomorphic ventricular tachycardia. In the second part, we will review the approach to polymorphic ventricular tachycardia.

Ventricular Ectopy and Monomorphic Ventricular Tachycardia

Premature Ventricular Complexes. Premature ventricular complexes can result from any of the previously described mechanisms: reentry, abnormal automaticity, or triggered activity. They are identified electrocardiographically by a wide QRS complex (>120 msec), but must be distinguished from supraventricular beats conducted aberrantly. A general evaluation including electrolyte measurements and a 12-lead electrocardiogram is indicated. However, unless the ectopy is associated with hemodynamic impairment, suppressive therapy and a reduction of inotropic or vasopressor support is rarely warranted. The long-term management of patients with premature ventricular complexes is guided by the same principles and rarely involves antiarrhythmic drug therapy.

Nonsustained Monomorphic Ventricular Tachycardia. Nonsustained monomorphic ventricular tachycardia may be caused by reentry, abnormal automaticity, or triggered activity. As stated for premature ventricular complexes, a limited evaluation is typically all that is required, and therapy is rarely necessary in the absence of symptoms or hemodynamic compromise. Again, withdrawal of vasopressors as tolerated in addition to correction of metabolic disturbances (particularly hypokalemia) may decrease the frequency and duration of nonsustained monomorphic ventricular tachycardia. Although the presence of nonsustained monomorphic ventricular tachycardia in the ICU has little immediate importance, it provides an opportunity to identify a potentially high risk group of patients amenable to primary prevention. In general, the long-term significance of nonsustained monomorphic ventricular tachycardia is related to the presence and severity of underlying structural heart disease. Indeed, in the absence of a reversible cause (electrolyte abnormality, recent myocardial infarction) patients with nonsustained monomorphic ventricular tachycardia, coronary artery disease, and decreased left ventricular ejection fraction (≤0.40) are at high risk for sudden cardiac death. Given the limited positive predictive value of even the best clinical variables, electrophysiologic testing provides an additional tool for risk stratification. Patients with inducible arrhythmias benefit from an implantable cardioverter-defibrillator (15, 16). Therefore, after recovery from acute illness, patients with persistent, nonsustained monomorphic ventricular tachycardia who also have coronary artery disease and an ejection fraction ≤0.40 should be evaluated with an electrophysiology study. If sustained arrhythmias are inducible, a cardio-
Ventricular tachycardia is reentry. The most common mechanism of ventricular tachycardia carries no increased risk for sudden death, it is not required only for debilitating symptoms. Ongoing randomized, controlled trials have demonstrated the superiority of implantable cardioverter-defibrillator therapy in improving survival in patients with sustained ventricular arrhythmias. The Antiarrhythmics Versus Implantable Defibrillator Trial, the Canadian Implantable Defibrillator Study, and the Cardiac Arrest Study in Hamburg evaluated the efficacy of implantable cardioverter-defibrillator therapy vs. drug therapy (usually amiodarone) in survivors of cardiac arrest and in patients with sustained monomorphic ventricular tachycardia associated with hemodynamic impairment (21–23). Therapy with an implantable cardioverter-defibrillator was found to be superior to drug therapy in both the Antiarrhythmics Versus Implantable Defibrillator Trial and Canadian Implantable Defibrillator Study, although the difference did not reach statistical significance in the Canadian Implantable Defibrillator Study. Preliminary results from the Cardiac Arrest Study in Hamburg trial further support the use of implantable cardioverter-defibrillators as primary therapy in survivors of near-fatal ventricular arrhythmias (24). Based on these results, we recommend that in the absence of a reversible cause, patients with sustained monomorphic ventricular tachycardia associated with syncope or left ventricular systolic dysfunction (ejection fraction ≤0.40) receive an implantable cardioverter-defibrillator (Fig. 2). In the setting of reversible causes, such as acute infarction or metabolic disturbances, no specific guidelines exist for long-term management because these trials specifically excluded such patients. Because the substrate for sustained monomorphic ventricular tachycardia may persist after correction of reversible factors, it is our recommendation that these patients undergo an electrophysiology study after the resolution of the acute illness. Com-

![Diagram of MONOMORPHIC VT]

Figure 2. Guidelines for the evaluation and treatment of monomorphic ventricular tachycardia. VT, ventricular tachycardia; MI, myocardial infarction; EF, ejection fraction; CAD, coronary artery disease; EPS, electrophysiology study; ICD, implantable cardioverter-defibrillator.
POLYMORPHIC VT

LONG QT INTERVAL or FEATURES of TDP

- Magnesium
- Rapid ventricular pacing or isoproterenol
- Correct underlying cause

NORMAL QT INTERVAL

- Acute MI
- No acute MI

No further evaluation

Reversible causes?

- (metabolic, acute ischemia, other critical illness)

YES

NO

Treat reversible causes

Evaluate underlying heart disease

Consider ICD based on relative contribution of above

cardiac catheterization 

+ revascularization 

EPS and ICD

Figure 3. Guidelines for the evaluation and treatment of polymorphic ventricular tachycardia. VT, ventricular tachycardia; TDP, torsades de pointes; MI, myocardial infarction; ICD, implantable cardioverter-defibrillator; EPS, electrophysiology study.

An appreciation of the synergistic interaction between substrate and functional factors in the critically ill patient is important not only for the immediate treatment of ventricular arrhythmias, but also in the formulation of future therapeutic plans.
tachycardia/ventricular fibrillation in the late phase of myocardial infarction carries a poor prognosis. Late polymorphic ventricular tachycardia/ventricular fibrillation characteristically occurs in patients in whom the MI has been complicated by severe heart failure or cardiogenic shock, and as such, the prognosis is usually determined by the hemodynamic status rather than the presence of arrhythmias. In selected patients, electrophysiology study or implantable cardioverter-defibrillator therapy may be considered. In the absence of myocardial infarction, acute ischemia remains a common cause of polymorphic ventricular tachycardia/ventricular fibrillation. Withdrawal of catecholamines (if tolerated) and anti-ischemic therapy with β blockers must be considered. In patients with severe coronary artery disease, revascularization or intra-aortic balloon counterpulsation may be required. If these measures are contraindicated because of critical illness, pharmacologic therapy with intravenous lidocaine or amiodarone may be used. Management of recurrent polymorphic ventricular tachycardia in the setting of critical illness is often very difficult. Decisions on revascularization must be based on the frequency and duration of polymorphic ventricular tachycardia, the relative contribution of primary ischemia vs. other proarrhythmic factors, and the risks of the intervention. Similar to the survivor of out-of-hospital cardiac arrest from ventricular fibrillation, the risk of recurrent polymorphic ventricular tachycardia in these patients is high and their long-term prognosis is poor. The Antiarrhythmics Versus Implantable Defibrillator Trial, Canadian Implantable Defibrillator Study, and Cardiac Arrest Study in Hamburg enrolled patients with resuscitated ventricular fibrillation and found a survival benefit with implantable cardioverter-defibrillator therapy. Of note, the Antiarrhythmics Versus Implantable Defibrillator Trial included a substantial number of patients with in-hospital cardiac arrest. Therefore, all patients with polymorphic ventricular tachycardia/ventricular fibrillation in the absence of long QTc or a reversible factor of sufficient magnitude to explain the arrhythmia must have an evaluation of left ventricular function and coronary artery disease. Ischemia should be treated, and most patients, particularly those with left ventricular systolic dysfunction, should have an implantable cardioverter-defibrillator placed if there are no contraindications.

CONCLUSIONS

An appreciation of the synergistic interaction between substrate and functional factors in the critically ill patient is important not only for the immediate treatment of ventricular arrhythmias, but also in the formulation of future therapeutic plans. Whereas short-term management during the acute illness is focused on correcting reversible factors and modifying the electrophysiologic milieu, the long-term approach must focus on identifying high-risk patients and preventing future arrhythmic events. Left ventricular systolic function remains one of the most important factors in determining the prognostic significance of ventricular arrhythmias. Ventricular arrhythmias in the absence of structural heart disease rarely have an impact on long-term prognosis. On the other hand, patients with left ventricular systolic dysfunction who develop ventricular arrhythmias in the setting of acute illness may remain at risk for sudden death because of the continued presence of the responsible substrate. A number of studies conducted over the last few years have expanded our understanding of arrhythmic death and highlighted the importance of implantable cardioverter-defibrillator therapy in patients with ventricular arrhythmias. Although most of these studies excluded patients with transient or reversible causes, we believe the approach to such patients in the setting of critical illness should be based on an understanding of the pathophysiology and the complex relationship between structure and function in the genesis of arrhythmias.

REFERENCES

17. Singh SN, Fletcher RD, Fisher SG, et al:
24. Kuck KH: Late-Breaking Clinical Trials. Atlanta, American College of Cardiology Scientific Sessions, 1998