Ventricular Arrhythmias, Part II: Special Concerns In Evaluation

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Abstract: In the initial installment of this series, the prevalence, significance, and indications for treatment of ventricular arrhythmias were discussed. In this section, we address special concerns in the evaluation of patients with ventricular arrhythmias including the importance of extracardiac and exacerbating factors, the likely role of silent myocardial ischemia, benefits and drawbacks of monitoring methods, proarrhythmic effect, and torsades de pointes. Treatment considerations and discussion of pitfalls in management will follow in the final two installments of this series. (J Am Bd Fam Pract 1988; 1:201-6.)

Importance of Extracardiac and Exacerbating Factors

Before proceeding to treat ventricular arrhythmias with medication, strong consideration should be given to identifying and trying to correct any extracardiac or exacerbating factors that may be present (Table 1). Stimulants (caffeine, nicotine, alcohol, diet pills), such sympathomimetics as those contained in over-the-counter cough and cold remedies, and recreational drugs may produce or exacerbate cardiac arrhythmias. Inquiring about the use of these agents therefore should be a routine part of the history. While the role of stimulants is frequently not a major one, at times it can be the primary factor responsible for producing an arrhythmia. Convincing the patient to eliminate such agents, at least for a trial period, is warranted and may be sometimes all that is needed to achieve control of the arrhythmia.

Emotional stress and insufficient sleep are two additional extracardiac factors to consider. Awareness of the problem, behavior modification, and the occasional use of a mild anxiolytic may be helpful if these factors are operative and obviate the need for antiarrhythmic therapy. Similarly, antiarrhythmic therapy may not be needed in cases where ventricular arrhythmias are precipitated by an underlying organic cause. In such instances, initial treatment should usually be aimed at correcting the underlying condition rather than reflexively starting antiarrhythmic therapy. For example, correction of electrolyte disturbances such as hypokalemia and hypomagnesemia, particularly in patients taking digitalis, frequently has a favorable effect on the arrhythmia. Similarly, in the presence of angina pectoris, coronary artery spasm, silent ischemia, or congestive heart failure, appropriate use of antianginal preparations, digitalis, or diuretics may lead to control of the arrhythmia. Failure to recognize the existence and importance of any of these extracardiac or exacerbating factors may frustrate the clinician and counteract even the most vigorous attempts at antiarrhythmic therapy.

The role of electrolyte disturbances in arrhythmogenesis is especially interesting. Studies have shown *hypokalemia* to be associated with an increased incidence in the frequency and complexity of ventricular arrhythmias in patients treated with diuretics.[1] This effect seems to be most marked in patients who have underlying heart disease.[2] During the acute phase of myocardial infarction, an inverse relation appears to exist between serum potassium levels and the presence of frequent and complex ventricular ectopy.[3] Hypokalemia in this setting has been shown to be an independent risk factor for the early occurrence of ventricular fibrillation.[4] Among survivors of out-of-hospital ventricular fibrillation, serum potassium values obtained immediately after resuscitation are significantly lower than serum potassium levels from ambulatory control patients who have underlying coronary artery disease.[5] This effect is not simply the result of preexistant diuretic use or acid-base status at the time of the arrest.[5]

Evidence points to catecholamines as playing an important part in producing ventricular arrhythmias with hypokalemia. The mechanism may be related to stress. Enhanced secretion of endogenous epinephrine is commonly seen in conditions of acute stress such as trauma, surgery,

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Table 1. *Extracardiac Factors and Exacerbating Causes of Ventricular Arrhythmias.*

Extracardiac Factors
Stimulants (i.e., caffeine, nicotine, alcohol, diet pills, over-the-counter cough/cold remedies containing sympathomimetics)
Stress
Insufficient sleep
Exacerbating Causes
Metabolic abnormalities (i.e., hypokalemia, hypomagnesemia)
Coronary artery disease (i.e., angina pectoris, coronary artery spasm, or silent ischemia)
Congestive heart failure

stroke, myocardial infarction, and intense emotional states.[6] In the laboratory, infusion of epinephrine to healthy volunteers in concentrations typical of those produced by these conditions significantly lowers serum potassium, often by as much as 1.0 mEq/L.[7,8] The effect appears to be specifically mediated by β-2 adrenergic receptors.[6,8-10] This is evidenced by the fact that cardio*selective* β-blockade (i.e., blockade of β-1 adrenergic receptors) does not prevent the effect, whereas nonselective β-blockade (with agents such as propranolol) effectively blunts the drop in serum potassium. Hypokalemia is not felt to be the result of an actual depletion of potassium from the body but, rather, to a shift of this cation from the extracellular to the intracellular compartment. Serum potassium begins to fall within minutes of the infusion and lasts for 1 to 2 hours after the infusion is stopped. When healthy volunteers are pretreated with diuretics for a week before epinephrine challenge, serum potassium levels are lowered even further.

Potential clinical implications of these experimental findings are obvious. Conditions known to produce acute stress (e.g., cardiac arrest, acute myocardial infarction, and the recovery period following these events) may be responsible for fluctuations in endogenous catecholamine secretion. This in turn may produce frequent transient episodes of stress-induced hypokalemia, predisposing these persons to an increased risk of ventricular arrhythmias. Persons with underlying heart disease and those taking digitalis or diuretics may be especially at risk. These considerations should provide at least a theoretical reason for favoring nonselective β-blockers in the treatment of ventricular arrhythmias, particularly for patients who are also receiving diuretics or for those who may be most prone to developing stress-induced hypokalemia.

The presence of *hypomagnesemia* may produce cardiovascular effects similar to those for hypokalemia.[11] In addition, hypokalemia is difficult to correct in the face of undetected hypomagnesemia. Because serum magnesium levels are not routinely included as part of the automated chemistry profile at most institutions, this condition commonly goes unrecognized. It appears to be present much more frequently than is generally appreciated, and in one series, it was found in more than 20 percent of hospitalized patients who had an associated electrolyte disorder (i.e., hypokalemia, hypophosphatemia, hyponatremia, or hypocalcemia).[12] Others in whom hypomagnesemia should be suspected include those with a history of alcohol abuse, malnourished patients, and patients receiving digitalis or diuretics.[11,12] Serum magnesium levels should be routinely checked if any of these predisposing factors are present.

Benefits and Drawbacks of Monitoring Methods

Methods of monitoring ventricular arrhythmias are shown in Table 2. Physical examination and cardiac auscultation are unreliable for distinguishing between premature beats that are supraventricular and those that are ventricular. The cheapest reliable method for documenting ventricular arrhythmias is to obtain a standard 12-lead electrocardiogram with a short rhythm strip. Unfortunately, this only monitors the cardiac rhythm for a short period of time. When one considers the commonly accepted definition of frequent ventricular ectopy (i.e., more than 10–30 premature ventricular contractions [PVCs] per hour or a PVC as infrequent as every few minutes), it becomes easy to see how even "frequent" PVCs may be overlooked by this method. On the other hand, if any PVCs are noted at all on a short rhythm strip, it is likely that both frequent and complex ventricular ectopy are present and would be detected if a longer period of monitoring was carried out.

In the past, Holter recordings of only a few hours' duration were used for arrhythmia detection. Although practical and economical, such recordings do not accurately reflect the severity of ventricular arrhythmias in many persons.[13] This is because of the tremendous *spontaneous variability* in PVC frequency that exists between one Holter recording and the next.[13,14] In one study, 57 pa-

Table 2. *Monitoring Methods and Their Drawbacks.*

Physical Examination and Cardiac Auscultation
Unreliable for distinguishing between supraventricular and ventricular premature beats
12-Lead ECG and Rhythm Strip
Only monitors rhythm for a short period of time
24-Hour Holter Monitor
Gold standard for monitoring
Completion of diary allows correlation of symptoms to occurrence of arrhythmias
Expensive ($200–$350 in most institutions)
May not identify person with infrequent but potentially lethal or lethal ventricular arrhythmias
Interpreter must be aware of the tremendous spontaneous variability in PVC frequency
May identify patients with silent ischemia
Transtelephonic Monitoring
Helpful in documenting arrhythmias that occur infrequently
Person must be aware of arrhythmias when they occur and must maintain consciousness long enough to transmit the arrhythmia
Patient History
Unreliable in persons who are unaware of ectopic beats
Potentially valuable in persons who can accurately sense ectopic beats (i.e., "poor man's Holter monitor")
Exercise Testing
Not nearly as sensitive as Holter monitoring in detection of ventricular arrhythmias
Demonstrates the effect of exercise (i.e., activity) on PVCs
May detect some forms of complex ventricular ectopy that are *not* picked up by Holter monitoring
Good screening test for underlying coronary artery disease
S-T segment depression in the absence of chest pain may alert the physician to silent ischemia

tients had three consecutive 24-hour Holter recordings performed during the late phase of acute myocardial infarction.[15] Ventricular tachycardia was detected in 12 of the 57 patients. When present, this arrhythmia occurred sporadically during the 72 hours of monitoring, and in only 1 of the 12 patients was ventricular tachycardia seen on all three 24-hour recordings. It was not present on 2 of the 3 days of the monitoring in 9 of the 12 patients.

Marked variability in PVC frequency also occurs in ambulatory patients with chronic ventricular arrhythmias. PVC frequency varies greatly from one day to the next, between successive 8-hour monitoring periods, and even from hour to hour within a single day.[16] Certain persons exhibit PVCs primarily during the day; others manifest them principally at night.[13,14] PVC frequency also varies with activity and emotional state. In many persons, however, marked spontaneous variability still will be seen even when monitoring conditions are kept absolutely constant.

Because of these fluctuations in PVC frequency, a monitoring period of at least 24 hours is usually recommended for adequate characterization of an arrhythmia. Monitoring for this duration of time permits recognition of diurnal variations in PVC frequency and allows detection of the maximal grade of ventricular ectopy.

Appreciation of the phenomenon of spontaneous variability in PVC frequency is essential if one is to interpret Holter recordings accurately and evaluate the effectiveness of antiarrhythmic therapy. Although a reduction in PVC frequency from 5,000 to 2,500 PVCs per day following institution of an antiarrhythmic agent would seem to suggest drug efficacy, one cannot statistically exclude spontaneous variation by this response. In order to do so, a reduction in PVC frequency of *at least* 80 percent between Holter recordings is required.[16] In this case, the number of PVCs would have to be decreased to less than 1,000 before one could safely conclude that the reduction was in response to the medication and not simply due to chance.

In general, persons with frequent ventricular ectopy almost always manifest complex forms. However, the converse does not necessarily hold true. Certain individuals with potentially lethal or even lethal ventricular arrhythmias only have infrequent ventricular ectopy between periods of ventricular tachycardia.[17,18] Malignant ventricular arrhythmias in these persons may thus go undetected if they do not occur on the day of monitoring.

An essential part of the Holter recording is the patient *diary*. When one considers how common ventricular arrhythmias are in the general population and how frequently patients come to a physician with symptoms suggestive of a cardiac arrhythmia, the importance of establishing a cause and effect relation between the two becomes evident. For example, if symptoms are noted at 10 a.m., 2 p.m., 5 p.m., and 11 p.m., but no cardiac arrhythmias are seen at these times, it is likely that symptoms are *not* cardiac related. Much useful information may therefore be obtained from Holter recordings even if no arrhythmias occur, provided that the diary is carefully filled out.

In symptomatic individuals who demonstrate cardiac arrhythmias on monitoring, one can infer

whether the arrhythmias are likely to be the cause of symptoms by their temporal relation to events noted in the diary. For example, if long runs of ventricular bigeminy occur while the patient is relaxed and totally unaware of the arrhythmia and palpitations or chest discomfort are only noted during periods of sinus rhythm, ventricular bigeminy is probably not related to the patient's symptoms.

The caveat is that no conclusions can be reached about the existence of a symptomatic arrhythmia unless symptoms occur on the day of monitoring. As noted above, patients may have malignant ventricular arrhythmias that only occur intermittently, sometimes as infrequently as every few weeks. In order to exclude this possibility, one would either have to extend the period of Holter monitoring or to consider another method for arrhythmia detection. Performing Holters for 2, 3, or more consecutive days until symptoms occur is cumbersome to the patient and expensive. A far more effective method for documenting the occurrence of sporadic ventricular arrhythmias is to employ transtelephonic monitoring. With this device, the patient is issued a set of electrode leads that may be kept at home for a period of days to weeks. When symptoms occur, the electrode leads are simply put on and a rhythm strip may be transmitted via telephone to the central monitoring station. The chief drawback of this method is that the patient must be aware of arrhythmias when they occur and be able to maintain consciousness long enough to transmit the rhythm.

An often ignored adjunct for monitoring is the *patient's perception of arrhythmia occurrence*. Although many persons are totally unaware of their arrhythmias, others are able to sense each and every ectopic beat that they have. In selected persons without life-threatening arrhythmias who have this awareness, and in whom electrocardiography has confirmed a temporal relation between symptoms and the occurrence of arrhythmias, the patient's account of symptoms may serve as a reliable and cost-effective adjunct for long-term monitoring. As such it may greatly reduce the need and expense of repeated Holter recordings for judging the effect of treatment (i.e., the "poor man's Holter monitor").

The final method for evaluating PVCs is stress testing. This modality demonstrates the effect that exercise has on the arrhythmia. In general, PVCs that diminish with progressively increasing degrees of activity tend to be associated with a better prognosis than those that are brought on by low levels of exercise. Although not nearly as accurate as Holter monitoring for quantitation and qualitative analysis of PVCs, complex ventricular arrhythmias (including ventricular tachycardia) with or without symptoms are sometimes elicited only by vigorous exercise.[18,19] In addition, the stress test serves as a nice screening tool for detecting the presence of underlying coronary artery disease. Holter monitoring and exercise testing are thus complementary procedures that provide different information, and both tests should be considered in the evaluation of patients with ventricular arrhythmias.[20]

Silent Myocardial Ischemia

In recent years, increasing importance has been attached to the finding of silent myocardial ischemia (SMI). Diagnosis is made by objective documentation of transient myocardial ischemia in the absence of chest pain or anginal equivalents.[21]

SMI is believed to be much more prevalent than is generally appreciated, occurring both in individuals who had previously been asymptomatic as well as in those with known coronary artery disease. Among the latter group, it is thought that silent ischemic episodes are far more common than episodes in which there is chest pain. Clinical implications are obvious. Because episodes of SMI are not alarming to the patient, they frequently go undetected and are left untreated. This predisposes the person to a significantly higher risk of morbidity from coronary artery disease.[21-23]

The modalities most commonly used for diagnosing SMI are Holter monitoring and exercise testing. At the present state of technology, detection is still problematic, especially when transient S-T segment depression is noted in otherwise asymptomatic persons without cardiac risk factors. In most such cases, these abnormalities reflect false-positive results. In contrast, when episodes of transient S-T segment depression are detected on Holter monitoring or during exercise testing in persons with multiple risk factors or known coronary artery disease, such findings are much more likely to represent true disease.

The reason detection of SMI is important in patients with ventricular ectopy is that ischemia may be the underlying (or exacerbating) cause of the arrhythmia. In such cases, treatment with nitroglycerin or calcium channel blocking agents may be far more appropriate than antiarrhythmic therapy.

Table 3. *The Proarrhythmic Effect.**

Baseline Frequency of PVCs per 24 hours	Degree of Increase over Baseline Frequency Needed to Declare Proarrhythmic Effect†
0–50 PVCs	10× increase
50–100 PVCs	5× increase
100–300 PVCs	4× increase
>300 PVCs	3× increase
Increased Complexity of PVCs	
Marked increase in ventricular couplets	
New development or marked increase in frequency of ventricular tachycardia	
Development of torsades de pointes	

*Adapted from Morganroth and Horowitz.[25]

†For example, if the baseline frequency of PVCs was 60 per 24 hours, a 5-fold increase (i.e., to at least 300 PVCs per 24 hours) would be needed to declare a proarrhythmic effect.

The Proarrhythmic Effect and Torsades de Pointes

Antiarrhythmic therapy is not benign. In 5–10 percent of patients treated with type IA antiarrhythmic agents (i.e., quinidine, procainamide, disopyramide), the drug makes the arrhythmia worse.[24] This paradoxical exacerbation in PVC frequency and complexity is known as the *proarrhythmic effect*. It occurs with all antiarrhythmic agents but appears to be less common when tocainide, mexiletine, or β-blockers are used.

The definition of a proarrhythmic effect varies depending on the baseline frequency of ventricular ectopy. When PVCs are infrequent, a much greater increase in their frequency is needed before one can conclude that a change is the result of a drug effect and not simply due to spontaneous variability. Guidelines have been suggested by Morganroth and Horowitz for defining this phenomenon (Table 3).[25] For example, if 200 PVCs are recorded on the initial day of monitoring and the patient is placed on an antiarrhythmic agent, the total number of PVCs would have to exceed 800 per day on the follow-up Holter (i.e., greater than a fourfold increase) before one could incriminate the antiarrhythmic drug as the cause of the increase. As indicated in Table 3, proarrhythmic effects may be defined not only by an increase in PVC frequency but also by aggravation of the complexity of ventricular ectopy. Examples include the more common occurrence of repetitive forms of PVCs and new development of ventricular tachycardia.

The final proarrhythmic effect to consider is torsades de pointes. First described in 1966 by the French physician Dessertenne, this unusual arrhythmia is most often caused by type IA antiarrhythmic agents that prolong the Q-T interval.[26] Toxic levels of a drug are not needed for the effect to occur.[27] As implied by the translation of its name (i.e., "twisting of the points"), this tachyarrhythmia is characterized by alternating polarity of the QRS complex about the baseline. It is often disturbingly resistant to therapy until the offending agent can be identified and eliminated. Consequently, type IA antiarrhythmic agents should be avoided in patients who have a prolonged Q-T interval before antiarrhythmic treatment is begun. If marked Q-T prolongation develops during therapy with these drugs, they should be immediately discontinued.

Proarrhythmic effects are probably much more common than many clinicians realize. Awareness of the existence of this phenomenon, prompt recognition of its occurrence, and immediate withdrawal of the offending agent are all essential to prevent exacerbation of the ventricular arrhythmia.

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