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Ectopic Ventricular Activity in a Cardiac Rehabilitation Program: Significance and Prognosis

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Abstract

Ventricular premature complexes (VPCs) are a frequent finding, even in patients without heart disease. There is an age-dependent increase in prevalence, and might be present in many structural heart diseases. VPCs are present in about 1% of routine ECGs, in up to 80% of 24-hour Holters and might be transiently present in 80 to 90% of patients after an acute myocardial infarction (AMI). The mechanisms by which they are generated include reentry, enhanced automaticity and triggered activity.

Despite highly prevalent, VPCs are most often asymptomatic and rarely have hemodynamic repercussion. Previously considered to be of minimal clinical significance, recent trials have reported an increased mortality in patients with VPCs. Exercise-induced VPCs (EVPCs) were also associated with an increased risk of adverse prognosis in several studies, especially when they occur during the recovery phase.

In patients with structural heart disease, frequent and complex VPCs represent markers of increased risk for malignant arrhythmias and death. After an AMI, frequent and/or multiform VPCs persisting more than 48 to 72 hours after the event resulted in increased long-term arrhythmic risk. The presence of repetitive EVPCs in a patient after an AMI is also associated with an increased risk of subsequent cardiac events.

The suppression of VPCs in asymptomatic patients is not currently recommended. In symptomatic patients, beta-blockers are the first-line therapeutic agent. If unsuccessful, antiarrhythmic medications or radiofrequency catheter ablation may be indicated.

In spite of the large number of studies addressing the prognostic implications of VPCs early after an AMI, studies evaluating their significance and prognostic implications during a cardiac rehabilitation program are lacking. As such, additional studies are required in order to optimize the prescription of rehabilitation program in patients with VPCs after an AMI.

Ventricular Premature Complexes: Prevalence and Clinical Features

Ventricular premature complexes (VPCs) are frequently encountered in a broad spectrum of the population, including patients with and without structural heart disease. Generally, VPCs present as solitary ectopic beats, however they may also occur in couplets or triplets (two or three successive ectopic beats), alternate with the sinus beat (bigeminy, trigeminy or quadrigeminy), or even in short runs (ventricular tachycardia). In patients with no known heart disease, VPCs occur in approximately 1% of routine ECGs [1] and in up to 80% of apparently healthy people during a 24-hour ambulatory monitoring [2,3]. In those with known or suspected coronary heart disease (CHD) submitted to an exercise stress test, exercise-induced VPCs (EVPCs) develop in about 7 to 18% of the patients [4,5].

The frequency of VPCs tends to increase with age and a higher prevalence has been reported in CHD,hypertension, and almost every form of structural heart disease. After an acute myocardial infarction (AMI), VPCs are seen in 80 to 90% of patients and have been related to residual ischemia [6], degree of residual coronary stenosis, left ventricular dysfunction and time since AMI [7].

Despite asymptomatic in the vast majority of those affected, palpitations or a feeling that the heart has stopped are the most frequent complaints. Occasionally, the patients may refer a pounding sensation in the neck, lightheadedness or near syncope. However, in patients with frequent ectopic activity associated with severely reduced left ventricular function or bradycardia, VPCs may decrease further the already compromised cardiac output resulting in significant hemodynamic compromise.

A special attention should be paid to catecholaminergic polymorphic ventricular tachycardia (CPVT), a rare (prevalence in Europe estimated to be 1:10 000), albeit frequently lethal, arrhythmogenic disorder that occurs in children and adolescents without structural heart disease and causes syncope and sudden death at a young age. The symptoms are almost always triggered by exercise or emotional stress and the arrhythmia is reproducibly induced during an exercise stress test as well as during isoproterenol infusion. The arrhythmia progressively appears after reaching a heart rate threshold (usually 120-130 beats per minute) occurring thereafter a progressive increase in VPCs frequency and complexity as heart rate increases. If the exercise is continued, salvas of polymorphic VT may appear and become more sustained and rapid, ultimately leading to syncope and in some cases degenerating into VF and sudden death [8].

Genesis of VPCs

VPCs are triggered from ventricular myocardium in a variety of

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situations and the mechanisms by which they are generated include reentry, enhanced automaticity and triggered activity [9]. Stimulants like nicotine, alcohol, caffeine, sympathomimetic agents or drugs like cocaine or amphetamines might also trigger VPCs.

VPCs are more common during or immediately after exercise. Sympathetic activation during vigorous exercise decreases ventricular tissue excitability threshold through several mechanisms: increased conduction velocity, decrease in myocardial refractory period, increased afterpotencials amplitude, and increase the slope of phase 4 spontaneous depolarization of the action potential. Other contributing mechanisms include metabolic acidosis and exercise-induced myocardial ischemia [9]. After exercise VPCs result from a rapid increase in vagal tone along with myocardial mechanoreceptor activation along with a brief, yet continuous, increase of norepinephrine plasma levels for several minutes after terminating the activity [9]. The aforementioned increase of VPCs during and after exercise, especially when frequent (>10% of all complexes or ventricular tachycardia) [10], can pose serious difficulties in prescribing and monitoring exercise for a cardiac rehabilitation program because the significance and prognostic value of such ectopic activity are not yet clearly established.

Ventricular tachycardia is classified according to its ECG morphology (monomorphic or polymorphic) and by its duration and consequences: sustained (lasting more than 30 seconds and/or causing hemodynamic compromise, which requires intervention) and nonsustained (lasting less than 30 seconds and not usually resulting in hemodynamic compromise). After an AMI, early ventricular tachycardia (VT) or ventricular fibrillation (VF), (occurring in the first 48 hours), usually results from reversible arrhythmogenic phenomena in the ischemic myocardium, however, the appearance of late VT or VF (after the 48 hour window) is related to the development of scar tissue, which creates areas of conduction block that can lead to the development of stable reentry circuits and hence promoting subsequent arrhythmias [9].

Prognostic Implications of VPCs

Although previously considered to be of minimal clinical significance in patients without a history of cardiac disease, recent studies have reported an increased mortality in patients with VPCs. The Atherosclerosis Risk in Communities (ARIC) study, find that those with a single VPC on a single two-minute ECG were more than two times as likely to die due to CHD than were those without VPCs [11]. A subsequent study from the same group found a two-fold increase in sudden cardiac death in patients with VPCs compared with those without VPCs [12]. Another study, that included 45 402 veterans, found that patients with VPCs on a resting ECG had a significantly higher all-cause mortality (22 vs 39 percent) and cardiovascular mortality (8 vs 20 percent) than those without resting VPCs [7].

The prognostic significance of frequent and/or complex VPCs in patients with apparently normal hearts also has yielded conflicting results. There are studies reporting similar outcomes in those who have frequent and complex VPCs compared to the general population [13], whereas others, particularly those analyzing the patients from the Multiple Risk Factor Intervention Trial (MRFIT) and the Framingham Heart Study, demonstrated a higher risk of mortality in patients with frequent or complex VPCs [14,15]. However, methods for exclusion of underlying structural disease differed between studies and might explain some of the inconsistency in the results.

VPCs morphology is considered a predictor of adverse outcome in CHD, although evidence for this assumption remains scarce. Ephrem et al. in a study that included patients referred for a 24-hour ambulatory Holter demonstrated that those with multiform VPCs were at a 4-fold increased risk for adverse outcomes in comparison to patients with uniform VPCs, regardless of the frequency [16]. In another study, the number of VPCs morphologies in a Holter recording also seems to be predictive of all-cause mortality [17]. The mechanism by which multiform VPCs are linked to worse prognosis remains unclear, although higher association with underlying structural disease or primary arrythmogenic conditions might account for increased mortality [18].

More recently, increased attention has been directed toward the prognostic significance of EVPCs [1,4,19-22]. At least four studies concluded that EVPCs, even in the absence of suspected CHD, were associated with increased risk of death during follow-up [1,20-22], whereas another found no association [22]. However, in the study of Jouven et al. only frequent VPCs (defined as a run of two or more consecutive VPCs or VPCs constituting more than 10 percent of all ventricular depolarizations during any of the 30-second ECG record) were associated with increased risk of death [1]. On the other hand, another study reported that only VPCs that occur during the recovery period after exercise were associated with an increased mortality risk, whereas EVPCs alone were not [4].

Even under beta-blocker therapy, asymptomatic VPCs usually persist on Holter recordings in patients with CPVT. Even though their complete suppression seems not to be mandatory, in the study of Hayashi et al. the presence of couplets or more successive VPCs during exercise testing was significantly associated with future arrhythmic events (sensitivity 0.62; specificity 0.67) [23].

In the presence of structural heart disease, VPCs are more common in three-vessel coronary artery disease, left ventricular function impairment associated with extensive segmental wall motion abnormalities and also in patients with higher degree of ST-segment depression during exercise stress test [5]. It has also been widely accepted that in those with structural heart disease, frequent and complex VPCs represent markers of increased risk for malignant arrhythmias and death [24].

As mentioned earlier, VPCs are a frequent finding after an AMI and frequent and/or multiform VPCs persisting more than 48 to 72 hours after an AMI, seems to be associated with an increased long-term arrhythmic risk. The presence of repetitive EVPCs in a patient after an AMI is also associated with an increased risk of subsequent cardiac events [9]. VT and VF are most frequent in the first hours after the infarction, however, the incidence of ventricular arrhythmias remains elevated for months or even years [9].

In the European Infarction Study (EIS) group, after an AMI, the presence of frequent VPCs (defined as >10 VPCs per hour) was associated with significantly increased mortality compared to those with no or few VPCs and the presence of more than 10 couplets per day was associated with a significantly higher mortality than the presence of only 1 to 10 ventricular couplets per day (22.2 vs 9.9 percent) [25]. Similarly, in the Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) group, the mortality rate was significantly higher in patients with frequent or complex VPCs compared to patients without VPCs and both frequent and complex VPCs were independently associated with increased six month mortality in multivariate analysis (RR 1.7, 95% CI 1.32 to 2.19) [26].

In the Canadian Assessment of Myocardial Infarction (CAMI) study, however, even though mortality increased progressively with more frequent VPCs, VPCs alone had no independent predictive value after multivariate analysis [27].

It is important to highlight that although there is a relationship between the frequency of VPCs and the severity of left ventricular impairment, an increased frequency of complex VPCs seems to be an important risk factor for adverse outcomes independently of the degree of myocardial damage [28,29].

In the past, the development of nonsustained VT (NSVT) was associated with an adverse prognosis, particularly when it occurred beyond the first several hours after an AMI [30], however, their incidence and prognostic significance seems to be lower with actual primary reperfusion therapies [31,32]. According to the results of the GISSI-2 group, after adjustment, the presence of NSVT on a 24-hour Holter before discharge was not associated with a worsening of the prognosis at six months (RR 1.20, 95% CI 0.80 to 1.79) [31]. However,

in a recent study that included 6 560 patients with non-ST elevation acute coronary syndrome, there was a higher risk of sudden cardiac death over the subsequent year in patients with 4 to 7 beats of NSVT (RR 2.3, 95% CI 1.5 - 3.5) and in patients with 8 or more beats of NSVT (RR 2.8, 95% CI 1.5 - 4.9) compared to those with no VT [33].

In contrast to NSVT, the development of late sustained arrhythmias is clearly associated with an increased risk of sudden cardiac death. On the other hand, in the case of early arrhythmias, the risk of long-term sudden cardiac death seems to vary with the type of arrhythmia. In fact, according to data from the Global Use of Streptokinase t-PA for Occluded Coronary Arteries (GUSTO-I) trial, in contrast to early-sustained monomorphic VT, early VF alone does not appear to predict adverse late outcomes [34]. This seems to suggest that, regardless the temporal relationship to infarction, sustained monomorphic VT may reflect myocardial scar and hence the presence of a fixed substrate that poses an increased long-term risk of arrhythmia recurrence and sudden cardiac death. In survivors of recent MI who have not had spontaneous VT or VF, monomorphic VT inducibility during electrophysiology studies seems to be associated with a higher risk of malignant arrhythmias and sudden death [35,36].

Treatment

Currently, the suppression of asymptomatic VPCs is not recommended because there is no clear evidence that their suppression improves survival. In patients with symptomatic VPCs with exposure to known stimulants, their removal should be the first measure to be taken.

If unsuccessful, a beta-blocker and/or a calcium channel blocker should be tried. Beta-blockers reduce symptoms by reducing the post-extrasystolic potentiation associated with VPCs. Because they do not exert direct effect on the myocardium, beta-blockers are not likely to suppress VPCs, except those due to increased catecholamines or excess sympathetic stimulation. However, is important to highlight that most patients with structural heart disease, like prior AMI or heart failure, are already under beta-blocker therapy as a part of the medical therapy specific to their disease.

In symptomatic patients that do not respond to the previous measures, antiarrhythmic medications or radiofrequency catheter ablation (RFA) may be tried. Class IC antiarrhytmic drugs, though highly effective at suppressing VPCs, are contraindicated in patients with prior ischemic heart disease due to the potential for proarrhythmia and increased mortality. In fact, as was demonstrated in the Cardiac Arrhythmia Suppression Trial (CAST), a randomized, placebo-controlled study which tested the hypothesis that suppression of asymptomatic or minimally symptomatic VPCs after myocardial infarction would reduce arrhythmic death, even though class IC drugs (encainide and flecainide) were effective in suppressing VPCs, they were associated with increased risk of arrhythmic dead (RR 3.6, 95% CI1.7 to 8.5) [37]. In symptomatic patients with prior AMI, amiodarone and sotalol are effective alternative agents. Although amiodarone seems to reduce VPCs and arrhythmic mortality in patients with a prior AMI or heart failure, its routine use in asymptomatic VPCs is not recommended because there is no evidence of significant improvement in overall mortality [38].

RFA may also be an alternative but it was shown to be beneficial only in patients with dilated cardiomyopathy or with right ventricular outflow tract related VPCs [39,40]. Multiform VPCs are unlikely to be responsive to RFA and medication is the only treatment option [16].

Finally, patients who developed late sustained ventricular arrhythmias after an AMI have a clear indication for an implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death. An ICD implatantion is also recommended in patients with CPVT that maintain syncope or documented sustained VT despite beta-blocker therapy [8].

Conclusion

VPCs are one of the most frequent findings during a cardiac rehabilitation program, however, their significance and prognostic implications remains largely unknown. Several studies have addressed this issue but heterogeneity and inconsistencies regarding classification of arrhythmias, population selection, structural disease assessment hinder more definitive conclusions. However, frequency (>10/hour) and complexity of ventricular arrhythmias are associated with higher potential for malignant arrhythmias and sudden death, even in asymptomatic subjects with no known structural heart disease.

Despite the large number of studies that addressed the importance of VPCs after an AMI, none have evaluated their implications in a cardiac rehabilitation setting, especially regarding exercise prescription and level of medical supervision and electrocardiographic monitoring during exercise training sessions. As mentioned earlier, VPCs are frequent during exercise and the presence of repetitive EVPCs after an AMI is linked to an increased risk of cardiac events. Further studies are warranted to establish the significance and approach to VPCs during exercise training sessions and whether autonomic changes secondary to exercise training have any impact over VPC frequency, complexity and prognosis.

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