



## Treating patients with ventricular ectopic beats

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# TREATING PATIENTS WITH VENTRICULAR ECTOPIC BEATS

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Ventricular ectopic beats (VEBs) are commonly seen in daily clinical practice. They are largely asymptomatic but can cause upsetting symptoms in some patients. In normal hearts, their occurrence is usually associated with no clinical significance. However, there are occasions where the presence of VEBs signifies a susceptibility towards more sinister arrhythmias, especially when heart disease is present. In some patients, VEBs are triggered by the same mechanism that gives rise to ventricular tachycardia which can be cured with catheter ablation. In addition, there are recent reports on the use of catheter ablation in cases where focal ventricular ectopics are found to trigger ventricular fibrillation. Appropriate clinical evaluation and investigations are important in assessing patients with VEBs so that effective treatment can be targeted when necessary. This article discusses the current knowledge and practice in this commonly encountered clinical cardiological problem.

## VENTRICULAR ECTOPIC BEATS: PAST, PREVALENCE AND PROGNOSIS

The first recorded description of intermittent perturbations interrupting the regular pulse, that could be consistent with VEBs, was from the early Chinese physician Pien Ts'io, around 600 BC, who was the master in pulse palpation and diagnosis.<sup>1</sup> He noted that these irregularities did not interfere with normal lifespan when they were occasional but an ominous prognosis was implied if they were frequent. This was shown to be so in more recent times where patients who have had a myocardial infarct were more prone to sudden death if they had frequent ventricular ectopics. Lown and colleagues<sup>2</sup> proposed a classification and grading of ventricular ectopics based on their frequency and complexity. This triggered the widely accepted dogma that increasing "severity" of ventricular ectopic activity was directly related to the risk of malignant ventricular arrhythmias and considerable effort had been spent in developing and employing antiarrhythmic drugs to suppress ectopics in the 1960s and '70s. This was set to change.

VEBs have been described in 1% of clinically normal people as detected by standard ECG and 40–75% of apparently healthy persons as detected by 24–48 hour ambulatory (Holter) ECG recording. Early studies had been criticised as the presence of heart disease was not investigated with stress testing, echocardiography or invasive tests. The study by Kostis *et al*<sup>3</sup> in 1981 in subjects free of recognisable heart disease, verified by the above list of investigations including right- and left-heart catheterisation and coronary arteriography, showed that 39 out of 101 subjects had at least one VEB over a 24 hour period and four subjects had > 100/24 hours, with five having > 5 VEBs in any given hour and four having multiform VEBs. Even frequent (> 60/h or 1/min) and complex VEBs occur in apparently healthy subjects, with an estimated prevalence of 1–4% of the general population.<sup>4</sup> These latter phenomena are often seen in patients with heart disease and are widely accepted as markers of increased risk of malignant arrhythmias and death. However, the study by Kennedy in 1985 suggested that in the absence of structural heart disease, even frequent and complex VEBs are associated with a benign prognosis.<sup>4</sup> Later, the study on a cohort of the Multiple Risk Factor Intervention Trial (MRFIT),<sup>5</sup> reported that the presence of VEB identified on a rest two-minute ECG rhythm strip was associated with a high risk for sudden death in apparently healthy subjects over a 7.5 year follow-up. Similar outcomes were reported in apparently healthy subjects in the Framingham Heart Study<sup>6</sup> whereby VEBs were associated with a twofold increase in the risk of all cause mortality, myocardial infarction and cardiac death. These results had been criticised for the lack of rigorous measures to exclude underlying heart disease which may have confounded the outcome.

### CAST study

The incidence and frequency of VEBs increase with age but studies had failed to establish a firm association between VEBs and arrhythmic death in older persons.<sup>5</sup> Both the increased prevalence of VEBs and the higher incidence of heart disease are likely to contribute towards the low specificity and predictive value of VEBs for arrhythmic death in this population. Furthermore, results of the Cardiac Arrhythmia Suppression Trial (CAST) published in 1989 questioned the

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causal importance of VEBs in increasing risk and revolutionised the thinking behind the necessity to suppress VEBs.<sup>7</sup> CAST was a randomised, placebo-controlled study which tested the hypothesis that suppression of asymptomatic or minimally symptomatic VEBs after myocardial infarction would reduce arrhythmic death. Although the class Ic drugs, encainide and flecainide, were effective in suppressing VEBs, arrhythmic death was more common in those treated with the drugs (4.5%) than placebo with a relative risk of 3.6. This study further highlights the proarrhythmic effect of these drugs in patients with heart disease and disputes the notion of using drugs simply for the sake of suppressing VEBs.

### HYPERTENSION, HYPERTROPHY AND VENTRICULAR ECTOPIC BEATS

It has been shown in early clinical studies that VEBs occur frequently in patients with hypertension. In the MRFIT population cohort of over 10 000 men aged 35–57 years, the level of systolic blood pressure was linked with the prevalence of VEBs. More recent data in the Atherosclerosis Risk in Communities (ARIC) study<sup>8</sup> of more than 15 000 African American and white men and women extended these findings to show that frequent or complex VEBs are also associated with hypertension. The Framingham study has indicated that patients with left ventricular hypertrophy by electrocardiographic criteria are at greater risk of sudden death and acute myocardial infarction than subjects with a normal heart. The ARIC Study also demonstrated that the prevalence of VEBs increases with the increased electrocardiographic estimate of left ventricular mass. These data communicate a consistent message that in patients with systemic hypertension there is a statistical relationship between VEBs and left ventricular hypertrophy and the latter is related to mortality, especially sudden death, in these patients.<sup>9</sup> There is ongoing debate as to whether VEBs in these conditions are genuinely specific markers for malignant arrhythmias or simply markers for the severity of the disease process, as in the case for other structural heart diseases, such as non-ischaemic dilated cardiomyopathy.

### CAFFEINE AND VENTRICULAR ECTOPICS

Caffeine is a central stimulant which can increase sympathetic activity. It is not illogical to assume that caffeine usage can increase the frequency of ventricular ectopics, especially if they may be fuelled by sympathetic activity. Clinical impression and anecdotes often associate arrhythmias with consumption of caffeine, alcohol and tobacco, and caution against these “pleasures” has been widely practised in managing patients with palpitation despite the relative lack of direct evidence. Animal studies had shown that caffeine administration at high doses can induce and increase the frequency of VEBs. Some epidemiological data exist with an association between VEB activity with caffeine intake, but experimental human studies have not produced consistent results to establish this link. The study by Prineas and colleagues<sup>10</sup> examined VEB occurrence in 7311 people who had a two-minute single lead ECG rhythm strip as part of a coronary risk factor screening programme. Persons who drank nine or more cups of coffee, or the equivalent amount of tea, per day were more likely to exhibit at least one VEB. The dose–response relationship was weak and there was a significant correlation between coffee consumption and other coronary risk factors. Dobmeyer and colleagues<sup>11</sup> performed electrophysiologic study in the presence of caffeine in seven

### Abbreviations

- ▶ **ARIC:** Atherosclerosis Risk in Communities
- ▶ **ARVD:** Arrhythmogenic right ventricular dysplasia
- ▶ **CAST:** Cardiac Arrhythmia Suppression Trial
- ▶ **ETT:** exercise tolerance test
- ▶ **ICD:** implantable cardioverter-defibrillator
- ▶ **MRFIT:** Multiple Risk Factor Intervention Trial
- ▶ **MRI:** magnetic resonance imaging
- ▶ **RVOT:** right ventricular outflow tract
- ▶ **VEB:** ventricular ectopic beat
- ▶ **VF:** ventricular fibrillation
- ▶ **VT:** ventricular tachycardia

normal volunteers and 12 heart disease patients. Caffeine did not affect cardiac conduction but did alter some of the electrophysiologic measurements with the conclusion that it might aggravate an existing predilection to arrhythmia. Many subsequent negative studies supported the notion that moderate ingestion of coffee does not increase the frequency or severity of cardiac arrhythmias.<sup>12</sup> Remarkably, one study by Graboys *et al* examined the effects of caffeine in 50 patients with known recurrent ventricular tachycardia, ventricular fibrillation and symptomatic non-sustained VT in whom no changes were seen with a modest dose of 200 mg of caffeine.<sup>13</sup>

On the other hand, caffeine restriction does not appear to have any significant effect on VEB frequency. DeBacker *et al* failed to demonstrate the efficacy of a “hygienic” intervention programme involving normal men with frequent VEBs.<sup>14</sup> Total abstinence from caffeine and smoking, reduction of alcohol intake along with exercise conditioning did not alter the occurrence or frequency of VEBs.

### VENTRICULAR ECTOPIC BEATS AND EXERCISE

Exercise testing is an established procedure widely used to diagnose myocardial ischaemia and to risk stratify patients with known coronary disease. It has also been used to evaluate ventricular arrhythmias as early as 1927. The conventional impression is that VEBs that are not provoked by exercise or reduce in activity during exercise can be regarded as “benign” and not of clinical significance. However, this notion has not been subjected to detailed scientific examination. What has been tested is the prognostic significance of VEBs induced either during or even after exercise.

Early studies did not establish an association between exercise induced VEB and prognosis over a relatively short follow up period (of around five years). The study by Jouven *et al*<sup>15</sup> in 2000 was the first comprehensive study to demonstrate an association between the occurrence of frequent VEB during exercise and a long-term increase in cardiovascular death. A total of 6101 asymptomatic French men free of clinically detectable cardiovascular disease were exercised and persons with frequent VEBs, defined as having > 10% of all ventricular depolarisations in any 30 s recordings during exercise, were found to have an increase in cardiovascular deaths by a factor of 2.67 after 23 years of follow up. It is interesting to note that 4.4% of all subjects had an ischaemic response to exercise and only 3% of these had frequent VEBs. Among subjects with frequent VEBs during exercise (2.3% of all subjects), only 5.8% had an exercise test positive for ischaemia. Multivariate analysis also demonstrated that the ischaemic response to exercise and

occurrence of frequent VEBs were independently associated with cardiovascular deaths. A recently published study in 2885 subjects who are offspring of the original Framingham study participants also presented similar findings.<sup>16</sup> Participants with VEBs at rest and chronic obstructive lung disease, in addition to other pre-existing cardiac conditions and usage of cardiac glycosides or  $\beta$  blocking agents, were excluded from the study, which may explain the low (0.1%) incidence of exercise-induced VEBs that exceeded 10% of all ventricular depolarisations. Hence, VEBs were defined as frequent when they exceeded the median of 1 VEB per 4.5 minutes of exercise (0.22 VEBs/min). Although it was concluded that exercise-induced VEBs were not associated with hard coronary heart disease events, both infrequent and frequent VEBs on exercise were associated with an increase in all-cause mortality over 15 years of follow-up.

The study by Frolkis *et al*<sup>17</sup> focused on the recovery period of the exercise test and showed that frequent VEBs after exercise were a better predictor of increased risk of death than VEBs occurring only during exercise. Frequent VEBs were defined by  $\geq 7$  VEBs per minute, ventricular bigeminy or trigeminy, ventricular couplets or triplets, torsade de pointes, ventricular tachycardia, flutter or fibrillation. Of the 29 244 patients referred for exercise testing without a history of heart failure, valve disease or arrhythmia, frequent VEBs during recovery were associated with a greater increased risk of death (hazard ratio 2.4) than frequent VEBs during exercise (hazard ratio 1.8) during a mean of 5.3 years of follow-up. After propensity matching for confounding variables, only frequent VEBs during recovery predicted an increased risk of death (adjusted hazard ratio 1.5). Similar results have also been shown in patients with heart failure. Inadequate vagal reactivation after exercise has been postulated to be the mechanism as vagal activity is known to suppress ventricular arrhythmia.

Although additional corroborative data are required from large cohort studies, these results have prompted the suggestion that frequent VEBs associated with exercise testing be considered as a new prognostic criterion in addition to ischaemia.

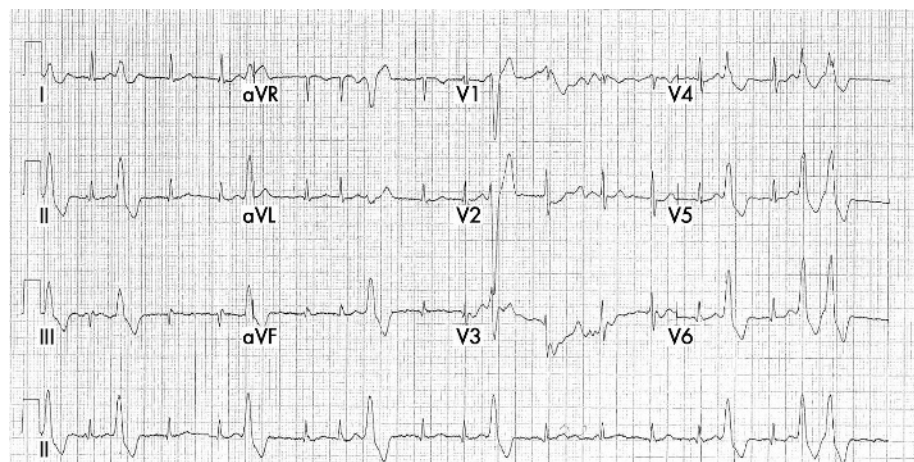
### RIGHT VENTRICULAR OUTFLOW TRACT TACHYCARDIA AND VENTRICULAR ECTOPIC BEATS

An exception to the above whereby exercise induced ventricular activity is associated with a relatively benign

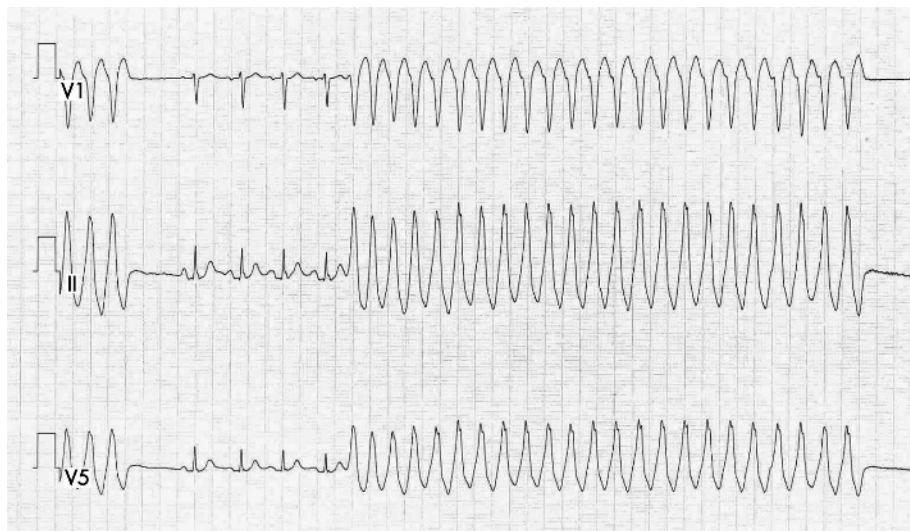
prognosis is the case of right ventricular outflow tract (RVOT) tachycardia. It belongs to the group of “idiopathic” ventricular tachycardias (VTs) or “normal heart” VTs—in the absence of overt structural heart disease—which arises from the RVOT. It is a common condition, with symptom onset between the second and fourth decade, being more common in women, and represents up to 10% of all VTs evaluated at specialised arrhythmia services.<sup>18</sup> VEBs originating from the RVOT have a distinctive ECG appearance with QRS complexes assuming a left bundle branch block, inferior axis morphology (fig 1). They may be identified on standard 12-lead ECG or ambulatory Holter recording as isolated VEBs, salvos or non-sustained VT. The arrhythmia mechanism is believed to be caused by cyclic AMP (adenosine monophosphate) mediated triggered activity. Exercise and emotional stress can increase the frequency of the VEBs or even induce non-sustained or sustained VT (fig 2). Many reports have suggested that long-term prognosis in patients with truly idiopathic RVOT-VT is excellent despite frequent episodes of VT, and sudden death is rare in patients with good biventricular function.<sup>18</sup> Indeed, right ventricular ectopics are more common than left ventricular ectopics in previous reports in patients with normal hearts<sup>3</sup> and it is likely that a majority of these right-sided VEBs were from the RVOT. Arrhythmogenic right ventricular dysplasia (ARVD) is a form of right ventricular cardiomyopathy where progressive, patchy fibrofatty infiltration of the right ventricle and subsequent ventricular dilatation provides an ideal arrhythmogenic substrate.<sup>19</sup> VT occurring in ARVD may mimic that of idiopathic RVOT tachycardia<sup>20</sup> but prognosis is much less favourable. It is important to distinguish between the two as RVOT tachycardia is now treated with curative catheter ablation,<sup>18</sup> whereas VTs in ARVD are best managed with the implantable cardioverter-defibrillator (ICD) as long-term results with catheter ablation are disappointing.

### Are all RVOT ectopics benign?

While catheter ablation for symptomatic idiopathic RVOT tachycardia is justifiable because of the high success and low complication rates,<sup>18</sup> the use of catheter ablation in treating isolated RVOT VEBs has been questioned due to the presumed “benign” nature of the VEBs. Recent studies using cardiac magnetic resonance imaging (MRI) have shown a high prevalence of focal fatty infiltration, thinning and segmental contraction abnormalities in the RVOT in patients



**Figure 1** Twelve lead ECG in a patient with ventricular ectopic beats originating from the right ventricular outflow tract.



**Figure 2** Continuous ECG recording in a patient with right ventricular outflow tract tachycardia in which non-sustained ventricular tachycardia was seen during exercise tolerance test.

with apparently idiopathic RVOT tachycardia.<sup>21</sup> Concern regarding an overlap between idiopathic RVOT ectopics and ARVD exists as the right ventricular infundibulum is commonly involved in ARVD.<sup>19</sup> However, there are reports that prognosis is good with no progression to ARVD in patients with monomorphic RVOT ectopics even with the presence of focal fatty replacement detected on cardiac MRI<sup>22</sup> or with morphological and functional right ventricular abnormalities detected on echocardiography.

In contrast to the data on the relatively good prognosis of RVOT ectopics, recent case reports have suggested that high grade RVOT ectopics can adversely affect left ventricular function. One series found haemodynamic signs of cardiac dysfunction in 45% of 47 patients with ventricular arrhythmias and no clinical evidence of heart disease.<sup>23</sup> Treatment of frequent RVOT ectopics by suppression with antiarrhythmic drugs<sup>24</sup> or elimination with catheter ablation<sup>25</sup> have been associated with significant improvement in cardiac performance. These data support a more proactive approach to the treatment of frequent RVOT ectopics, especially in the presence of left ventricular dilatation and/or dysfunction.

The benign nature of RVOT ectopics is further challenged by recent data that the RVOT can be the site of origin of ectopics triggering polymorphic VT and ventricular fibrillation.<sup>26</sup> These ectopics were found to be short-coupled, sometimes falling on the T wave of preceding beats, and the ventricular rate during polymorphic VT was faster (220–280 beats/min) than the rate of monomorphic VT seen in idiopathic RVOT tachycardia (< 230 beats/min). Catheter ablation has been shown to be effective and an aggressive approach has been recommended if there is a history of syncope, if VEBs are short-coupled and very frequent, and if the VEBs are associated with very fast VT.

#### “MALIGNANT” VENTRICULAR ECTOPIC BEATS

As described in the previous section, ectopics originating from the RVOT have been associated with malignant ventricular arrhythmias. The ability of frequent VEBs originating from a focal source in triggering idiopathic ventricular fibrillation (VF) in seemingly normal hearts was first reported by Haissaguerre *et al.*<sup>27</sup> The VEBs were mapped to sites at the RVOT and also along the distal Purkinje system in both left and right ventricles. Catheter ablation was shown

to be effective in acutely eliminating VEBs and reducing the incidence of further VF recurrence.<sup>28</sup> Similar triggers have been shown in selected patients with long QT and Brugada syndromes with report of successful elimination of VEBs with catheter ablation. Further studies in large numbers of patients with longer follow up are required to assess the full prognostic benefit of this approach.

Catecholaminergic polymorphic ventricular tachycardia is a rare condition whereby mutations in the cardiac ryanodine receptor and calsequestrin, which are key calcium handling proteins in the cardiac ventricular myocyte, cause malignant ventricular arrhythmias induced by catecholamines. Progressive VEBs are induced with exercise or stress which can cause syncope or sudden death with polymorphic VT or VF. Treatment is usually with  $\beta$  blockers and ICD implantation.

#### APPROACH TO TREATING PATIENTS WITH VENTRICULAR ECTOPICS

Patients with VEBs often describe “missing a beat” or “feeling the heart has stopped”, being aware of the compensatory pause following VEBs, as well as “extra beats” or “thumps”. The frequency and severity of these symptoms should be assessed. The presence, duration and frequency of any fast palpitation should be noted and any association with pre-syncope or syncope recorded. Patients should be asked about any triggering factors, especially exercise. The presence of ischaemic or structural heart disease should be considered, taking clues from past medical history and other cardiac symptoms, especially those suggesting the presence of heart failure. Caffeine, alcohol, and drug intake should be noted as well as smoking habits. Family history may be relevant especially if there has been sudden death or other clues towards a genetic syndrome or cardiomyopathy. Clinical examination should be aimed at identifying any structural heart disease and/or heart failure.

In the absence of heart disease or significant risk factors, patients with symptoms of VEBs that are self-limiting or respond to lifestyle modifications may simply be reassured while patients with ongoing or worsening symptoms should undergo further investigations. These include a resting 12-lead ECG, echocardiography, ambulatory Holter recording and exercise tolerance test (ETT). Echocardiography is

important as both ventricular function and the presence or absence of structural heart disease are important considerations in assessing the need for further intervention and treatment. The morphology of VEBs should be assessed in all the available rhythm recordings including 12-lead ECG, Holter recording and ECG during ETT. It should be determined if the VEBs are coming from a single focus (unifocal) or from many sites (multifocal). Repetitive unifocal activity, especially associated with exercise, is suggestive of triggered activity primed by catecholamines, and the presence of monomorphic VT, whether non-sustained (< 30 s) or sustained (> 30 s), should be sought. VEBs which reduce in frequency on exercise are generally regarded as “benign” while multifocal VEBs provoked on ETT may signify an underlying risk of cardiac disease even in the absence of conventional ischaemic changes (see above).

### Treatment for patients with VEBs

In considering the need for further intervention and planning treatment for patients with VEBs, it is important to consider: (1) whether there is underlying heart disease; (2) the frequency of the VEBs and if VT has been documented; and (3) the frequency and severity of symptoms. Table 1 summarises a treatment approach based on these factors.

In the absence of heart disease and if VEBs are infrequent or reduce in frequency on ETT, with no documented VT, patients should be reassured and no specific treatment is required—especially if they are relatively asymptomatic. The same patients with significant symptoms should have their blood pressure checked and investigated and treated if high. Patients with high caffeine intake should be advised to try decaffeinated drinks and/or reduce caffeine consumption to assess the impact on symptoms. If these measures fail  $\beta$  blockers may be considered, but a balance should be struck

### Treating patients with ventricular ectopic beats: key points

- ▶ Ventricular ectopic beats (VEBs) are frequently seen in daily clinical practice and are usually benign
- ▶ Presence of heart disease should be sought and, if absent, indicates good prognosis in patients with VEBs
- ▶ There is no clear evidence that caffeine restriction is effective in reducing VEB frequency, but patients with excessive caffeine intake should be cautioned and appropriately advised if symptomatic with VEBs
- ▶ Unifocal VEBs arising from the right ventricular outflow tract are common and may increase with exercise and cause non-sustained or sustained ventricular tachycardia. Catheter ablation is effective and safe treatment for these patients
- ▶  $\beta$  blockers may be used for symptom control in patients where VEBs arise from multiple sites. It should also be considered in patients with impaired ventricular systolic function and/or heart failure
- ▶ Risk of sudden cardiac death from malignant ventricular arrhythmia should be considered in patients with heart disease who have frequent VEBs. Implantable cardioverter-defibrillator may be indicated if risk stratification criteria are met
- ▶ VEBs have also been shown to trigger malignant ventricular arrhythmias in certain patients with idiopathic ventricular fibrillation and other syndromes. Catheter ablation may be considered in some patients as adjunctive treatment

**Table 1** An approach to the treatment of patients with ventricular ectopic beats

| Structural heart disease | Frequent VEBs or VT | Frequent symptoms | Treatment                                     |
|--------------------------|---------------------|-------------------|---|
| –                        | – (↓ on exercise)   | –                 | Reassure                                      |
| –                        | –                   | +                 | $\beta$ blocker                               |
| –                        | + (monomorphic)     | ±                 | Catheter ablation                             |
| +                        | –                   | ±                 | 1. Assess SCD risk<br>2. $\beta$ blocker      |
| +                        | +                   | ±                 | 1. $\beta$ blocker<br>2. ICD if high SCD risk |

ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; VEB, ventricular ectopic beat; VT, ventricular tachycardia.

between the level of symptoms and the possibility of side effects, given that VEBs in the absence of heart disease carry a good prognosis. There is no evidence to support the use of other antiarrhythmic agents simply for the sake of suppressing VEBs, especially considering their proarrhythmic (for example, flecainide<sup>7</sup>) and other side effects (for example, amiodarone).

In patients with normal hearts where there are frequent unifocal VEBs, especially if salvos or VT are induced on exercise, catheter ablation should be considered. Results are favourable especially if the VEBs arise from the RVOT. Similar focal VEBs may also originate from other parts of the right ventricle and also the left ventricular outflow tract and sinuses of Valsalva which are also amenable to catheter ablation.<sup>29</sup>

In the presence of heart disease, especially if there is impaired ventricular systolic function and/or symptoms of heart failure, the presence of VEBs may signify an arrhythmogenic risk or reflect the severity of the underlying cardiac disease. Even in the presence of infrequent VEBs, appropriate consideration should be given as to the risk of sudden cardiac death in these patients.  $\beta$  blockers may be effective in reducing the frequency of VEBs and symptoms in some patients. If there are frequent VEBs or non-sustained VT, patients should be treated with  $\beta$  blockers<sup>30</sup> and considered for ICD implantation if sudden death risk from malignant ventricular arrhythmia is high.

Additional references appear on the *Heart* website—<http://www.heartjnl.com/supplemental>

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Additional references appear on the *Heart* website—<http://www.heartjnl.com/supplemental>