Review Article

# Programmed Ventricular Stimulation – Indications and Limitations: A Comprehensive Update and Review

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Programmed ventricular stimulation (PVS) was introduced in 1968 as a means of identifying patients at high risk of sudden cardiac death.[1] Nowadays, sudden cardiac death is still difficult to prevent and a strategy for identifying patients at high risk requires a major public health investment along with institutional and physician awareness. PVS is a relatively safe procedure when performed under carefully controlled conditions. Therefore, appropriate implementation and interpretation of PVS is essential from the perspective of efficacy and cost-effectiveness.[2]

Some reports have questioned the usefulness of PVS nowadays,[3,4] asking what electrophysiological studies still have to offer, and whether we still need PVS. This review aims to pinpoint the value and benefit of PVS and to clarify under which medical conditions it is still valid, in light of the currently available scientific data.

## Methods

### Data collection

Original and review articles indexed in Pubmed since 1970 and found consistent with the study objective were retained; generic terms consisted of "programmed ventricular stimulation" and "electrophysiological study". A systematic synthesis and review was performed with special emphasis on the clinical implication of each article.

### Technique and criteria of positivity of PVS

Classically, the main criterion of positivity is the induction of sustained monomorphic ventricular tachycardia (SMVT);[5,6] nevertheless, induction of other forms of ventricular arrhythmias (VA) such as polymorphic fast ventricular tachycardia (VT), ventricular flutter, or ventricular fibrillation (VF) can be of clinical significance depending upon the clinical context.[5,7,8]

Few data are available in humans regarding the value of PVS in patients without structural heart disease, but studies performed on the normal canine heart[9] showed that VF can only be induced with very aggressive protocols, using both right and left ventricle, up to 3 extrastimuli with a short coupling interval, and combining a high pulse width (up to 4 ms) with high current strengths (up to 15 times the diastolic threshold).

The type of the inducible VA is correlated with the underlying mechanism; SMVT is common in ischaemic heart disease with old scar that forms a substrate for re-entry,[10] whereas polymorphic VT

and VF are more likely to be encountered when a focal mechanism is present, such as triggered activity and/or enhanced automaticity.[5]

### *Mode of stimulation*

The standard method consists of the extrastimulus mode,[11] using an 8-beat drive train at the right ventricular apex and outflow tract, with the addition of one or more extrastimuli at baseline, the shortest prematurity (coupling interval) being above 180 ms in order not to induce VF;[7] there are two protocols of stimulation, the 6-step and the 18-step protocol (Table 1); both protocols use an 8-beat drive train and an average of 4 seconds' inter-train pause. The 6-step protocol starts with coupling intervals of 290, 280, 270 (+/- 260 = S4), that are shortened simultaneously in 10-ms steps until inducibility or refractoriness. The 18-step protocol uses 1, 2, then 3 extrastimuli in conventional sequential fashion; the active coupling interval is shortened until refractoriness, while passive coupling intervals are kept sequentially at 10 ms above refractoriness (Figure 1); Current data do not show any superiority of one protocol over the other regarding inducibility: nevertheless, the 18-step protocol is considered more practical and so is better recommended.[11] Figure 2 is a classical representation of an 18-step protocol that induces a rapid VT with 2 extrasystoles.

The test can be made more sensitive with isoproterenol infusion. This is particularly helpful for induction of VA with triggered activity,[12] while burst pacing (atrial and ventricular) is useful for induction of VA with a focal mechanism. When the patient is not inducible with apical right ventricular stimulation, the test must be repeated at the right ventricular outflow tract or the septum. The introduction of short-long-short sequences of burst pacing can help the induc-

**Table 1.** The 18-step and the 6-step ventricular stimulation protocols.

| RVA | RVOT | DTCL | ES |
|---|---|---|---|
| 1 | 10 | 600 | 1 |
| 2 | 11 | 600 | 2 |
| 3 | 12 | 600 | 3 |
| 4 | 13 | 400 | 1 |
| 5 | 14 | 400 | 2 |
| 6 | 15 | 400 | 3 |
| 7 | 16 | 350 | 1 |
| 8 | 17 | 350 | 2 |
| 9 | 18 | 350 | 3 |
| RVA | RVOT | DTCL | ES |
| 1 | 4 | 600 | 3 |
| 2 | 5 | 400 | 3 |
| 3 | 6 | 350 | 3 |

RVA, right ventricular apex; RVOT right ventricular outflow; DTCL drive train cycle length; ES, extrasystole

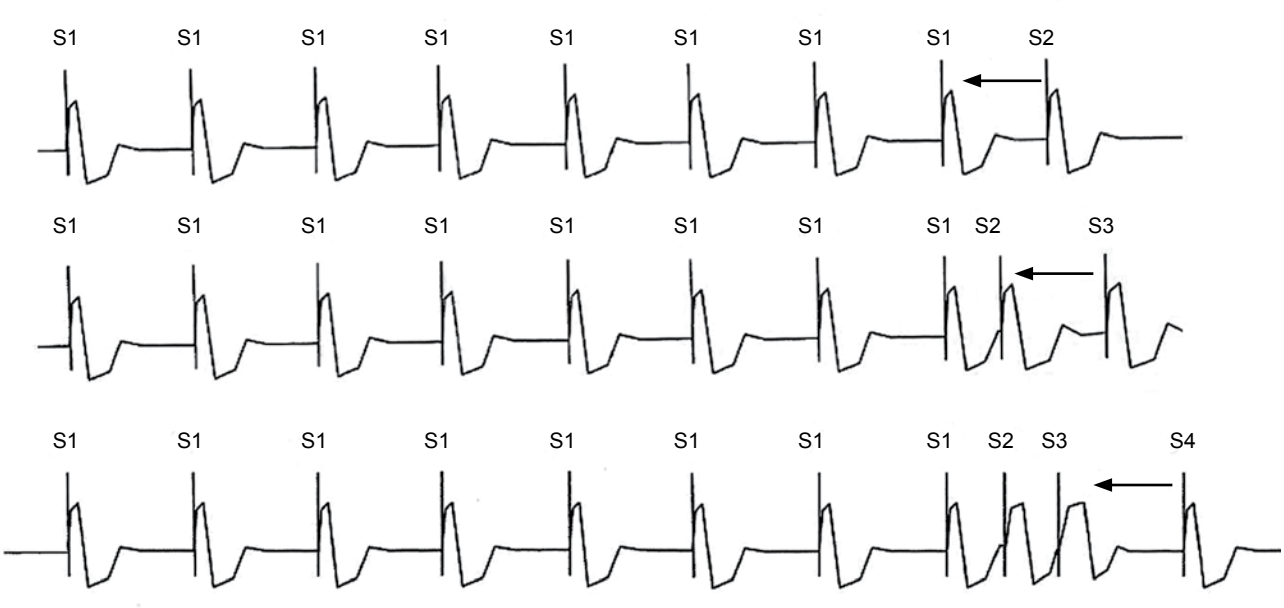


**Figure 1.** Eighteen-step protocol with sequential increase in extrastimuli and progressive shortening of the active coupling interval, while the passive coupling intervals are kept at 10 ms above refractoriness.

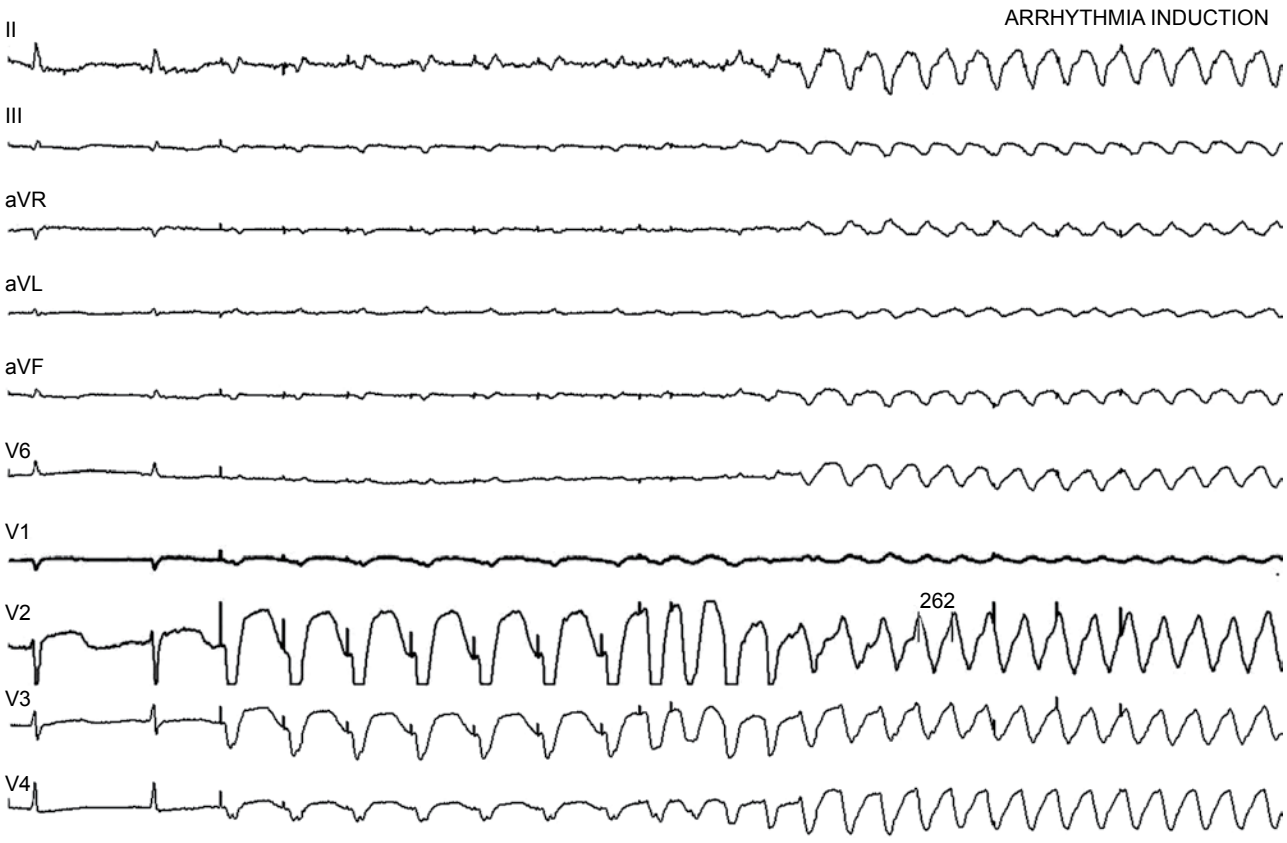


**Figure 2.** Induction of fast ventricular tachycardia (cycle length 262 ms) with the use of two extrastimuli (S1-S2, S3) after a drive train of 8 beats (shown are surface ECG leads).

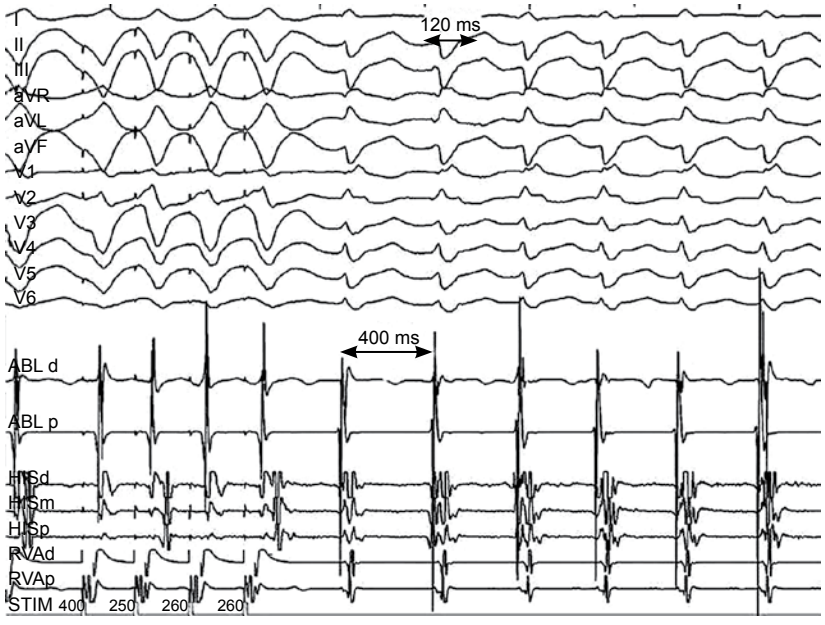


**Figure 3.** Induction of left posterior fascicular ventricular tachycardia from the right ventricle (S1=400 ms, S2=250 ms, S3=260 ms, S4=260 ms; right bundle branch block pattern and left axis deviation; tachycardia cycle length ~400 ms; QRS duration 120 ms). The ablation catheter located in the left ventricle shows pre-activation compared to the right ventriculogram and to the surface QRS.

tion of bundle branch re-entry VT. Also left ventricular stimulation may be required for the induction of some VA-like fascicular tachycardia when right ventricular stimulation is judged not efficient; Figure 3 shows a fascicular tachycardia induced from the right ventricle.

The intensity of the current may decrease the refractoriness threshold and accordingly may induce VF or polymorphic VT; a current of 5 mA is usually sufficient to reliably identify most patients who have symptomatic VA.[14] The delivery of a fourth extrastimulus may significantly increase the yield of PVS and should be considered only at the end of the protocol (18-step) in order to prevent induction of polymorphic VT or VF.[15] The drive cycle length also affects the outcome; inducibility increases as the basic drive cycle length shortens.[16] PVS can be performed "non-invasively" via the implanted cardioverter/defibrillator (ICD) in selected patients (testing of VA inducibility and/or testing of device efficacy). Serial electrophysiological testing has largely been abandoned and the ICD has proven to be significantly more efficient than anti-arrhythmic drug therapy for prevention of sudden cardiac death.[17]

## Results and discussion

Of the studies reviewed, 52 were retained and a systematic analysis was performed accordingly with special focus on clinical implications. Table 2 summarises the major studies with regard to cardiomyopathy and outcome.

### *PVS in ischaemic heart disease*

In this setting, left ventricular systolic function plays a fundamental role. One important landmark study is MADIT I,[18] which showed a significant value for PVS in stratifying patients at high risk of sudden cardiac death, this study included patients with prior myocardial infarction, left ventricular ejection fraction ≤35%, NYHA class I-III, and with asymptomatic non-sustained VA. Another point of reference in this setting is the MUSTT study,[19] which tested the value of PVS in patients with coronary artery disease, having an ejection fraction ≤40% and with non sustained VA; this study showed that PVS is an important risk stratifier for malignant VA. Later a sub-study of MUSTT[20] demonstrated a poor prognostic value of serial electrophysiological testing and showed that the characteristics of the non-sustained VA (morphology, grade, rate, duration) did not correlate with inducibility.[21]

The MADIT-II[22] study showed significantly improved survival with prophylactic implantation of an ICD, and without screening for VA inducibility, in a population of patients with previous myocardial infarction and left ventricular ejection fraction <31%. However, a MADIT II[23] sub-study showed that many

**Table 2.** Main studies (author, year, cardiopathy, population, outcome) regarding PVS.

| Author | Year | Cardiopathy | Population | Issue studied/outcome |
|---|---|---|---|---|
| Wellens HJ et al | 1972 | Non-specific | 5 | VT induction |
| Belhassen B et al | 1982 | Non-specific | 9 | Effect of supraventricular beats |
| Brugada P et al | 1984 | Non-specific | 102 | Effect of number of extrastimuli |
| Bhandari AK et al | 1985 | Long-QT Syndrome | 15 | Limited value of PVS |
| Weissberg PL et al | 1987 | Non-specific | 70 | Effect of current intensity |
| Avitall B et al | 1992 | Non-specific | 146 | Induction of VT versus ventricular fibrillation |
| Hummel JD et al | 1994 | CAD | 209 | Effect of number of extrastimuli |
| Fisher JD et al | 1994 | Non-specific | 84 | Tandem versus simple sequential method |
| Moss AJ et al (MADIT) | 1996 | CAD | 196 | ICD versus medical therapy |
| Buxton AE et al (MUSTT) | 1996 | CAD | 1480 | Non sustained ventricular arrhythmia |
| Capucci A et al | 2000 | Non-specific | Review | Role of EP guided therapy |
| Schmitt C et al | 2001 | CAD | 1436 | Value of PVS with non invasive markers |
| Moss AJ et al (MADIT II) | 2002 | CAD | 1232 | Prophylactic ICD implanted without PVS |
| Becker R et al | 2003 | DCM | 157 | Value of PVS in DCM |
| Brugada J et al | 2003 | Brugada syndrome | 547 | Significance of inducibility |
| Khairy P et al | 2004 | Tetralogy of Fallot | 252 | Significant value of PVS |
| Ashwath ML et al | 2005 | Baseline QRS width | 137 | Higher inducibility with wide QRS |
| Paul M et al | 2007 | Brugada Syndrome | Meta-analysis | Equivocal role of PVS |
| Daubert et al | 2009 | DCM | 204 | Inducibility predicts subsequent ICD use |
| Rolf S et al | 2009 | DCM | 160 | Value of inducible Ventricular Fibrillation |
| Steffel J et al | 2009 | LV non-compaction | 24 | Inducibility low |
| Mehta D et al | 2011 | Sarcoidosis | 76 | Significant value of PVS |

VT – ventricular tachycardia; PVS – programmed ventricular stimulation; CAD – coronary artery disease; ICD – implantable cardioverter defibrillator; EP – electrophysiology; DCM – dilated cardiomyopathy; LV – left ventricle.

factors correlate with higher inducibility: lower heart rate, lower ejection fraction and a longer time interval since myocardial infarction. In addition, inducibility was associated with more utilization of the ICD for VT and less for VF;[24] also the absence of inducibility did not predict a good prognosis in this setting.[25]

### *PVS in idiopathic dilated cardiomyopathy*

The reliability of PVS in patients with idiopathic dilated cardiomyopathy is poor.[26] According to the SCD-HeFT study, patients with severe systolic dysfunction are at high risk of sudden cardiac death and are eligible for ICD implantation as prophylactic therapy without the need for PVS.[27] Nevertheless, this finding raises many concerns and questions: does this imply a "systematic" implantation of an ICD for all patients with an ejection fraction <35%? A recent study stated that the majority of heart failure patients who have an ICD implanted as prophylactic therapy based only on ejection fraction would never experience an arrhythmic event requiring device intervention over several years of follow up.[28] Consequently, the same authors suggested that more arrhythmogenic markers should be implemented for better risk stratification of sudden cardiac death, including autonomic tone, heart rate variability and turbulence, QRS duration, late potentials, QT dynamicity and markers of collagen turnover.

The mechanism of arrhythmia is correlated with the type of inducible VA; it is now well established that induction of SMVT is due to the presence of a macro–re-entry, usually consecutive to ischaemic scar or fibrosis, whereas polymorphic VT and/or VF occur mainly in non-ischaemic cardiomyopathy and are due to a focal mechanism.[29,30] One special type of VA occurring in this setting is bundle branch re-entrant ventricular tachycardia. This arrhythmia is usually inducible with PVS, while electrophysiological studies may be used to confirm the mechanism and to guide ablation.[31] Finally, non-inducibility does not necessarily predict a good prognosis in idiopathic dilated cardiomyopathy. In addition, SMVT is not the only criterion of positivity; polymorphic VT or VF are also reliable outcomes in this setting.[32]

### *PVS in other conditions*

PVS is of limited value in VT originating from the papillary muscles, whether posterior[33] or anterior,[34] given that most of these VA have a non re-entrant mechanism. Idiopathic VT usually originates from the outflow tract, and mostly occurs in the setting of a "normal" structural heart. Idiopathic left VTs are categorised into three subgroups:[35] verapamil-sensitive intrafascicular (demonstrates entrainment and is mediated by re-entry); adenosine-sensitive (mediated by triggered activity); and propranolol sensitive (mediated by a focal mechanism). The heterogeneity of the mechanisms of these arrhythmias explains the variable PVS yield in idiopathic left VT. Idiopathic right VT is mainly mediated by triggered activity, and inducibility is non consistent, even with catecholamine infusion.[36]

PVS in patients with idiopathic VF yields inconsistent inducibility (50-60%).[37,38] A "loss-of-function" or mutation in SCN5A genes is common in patients with idiopathic VF (and in some patients with early repolarisation syndrome) and this phenomenon predisposes to idiopathic VF.[38]

The value of PVS in patients with non-sustained VA is variable and inducibility depends on the underlying mechanism.[39] For patients who have survived an episode of sudden cardiac death, PVS has a variable yield, and most importantly, non-inducibility does not predict a good prognosis.[40] For patients presenting with syncope of unknown origin, PVS is to be considered only when non-invasive testing does not lead to a specific aetiology, especially in the setting of structural heart disease.[41] Interestingly, in a series of patients presenting with syncope of unknown origin,[39] non-sustained VA was found to be independently associated with mortality, and PVS identified patients at high risk of sudden cardiac death.

Studies assessing the value of PVS in Brugada syndrome yield conflicting results: an initial study[42] showed that inducibility was a marker of poor prognosis, but more recent reports[43,44] stated that inducibility was not a predictor of adverse events; both these studies found that a history of syncope, a spontaneous type I electrocardiogram, ventricular refractory period <200 ms, and QRS fragmentation were rather significant predictors of malignant VA. PVS in left ventricular non-compaction has a limited value; a recent study[45] showed that PVS was specific but had low sensitivity in this setting. The usefulness of PVS in arrhythmogenic right ventricular dysplasia is debated. Most VA in this setting have a re-entry mechanism; nevertheless PVS has a limited value,[46] given the relatively rapid and unpredictable evolution of this cardiomyopathy, and the ICD is the preferred management tool, regardless of the PVS results.

In patients with hypertrophic cardiomyopathy, the value of PVS is limited. Inducibility is not specific and is not listed among the prognostic factors for stratifying high risk patients, while non-inducibility does not predict a good prognosis.[47] In repaired tetralogy of Fallot, PVS has a diagnostic and prognostic value for risk stratification; inducible sustained polymorphic VT should not be considered as non-specific VA in this setting.[48] Patients with bundle branch block, regardless of the underlying heart disease, were found to have higher inducibility[49] compared to those who had a narrow QRS. In patients with sarcoidosis with evidence of cardiac involvement, PVS enables the identification of patients at risk of malignant VA.[50] In long-QT syndrome, PVS is of limited value,[51] whereas the role of PVS in short-QT syndrome is more consistent,[52] with atrial fibrillation and polymorphic VT easily inducible. Catecholaminergic polymorphic VT is an inherited channelopathy with a disorder of myocyte calcium homeostasis predisposing to VA, which is easily inducible with an exercise test and after isoproterenol infusion during PVS.[52]

### *Clinical implications*

PVS is essential to assess the inducibility and the mechanism of many VA. Accordingly, management can be guided with regard to the clinical setting in order to prevent sudden cardiac death. Management of patients with VA should be individualised according to the nature and severity of the underlying heart disease.[53] Radiofrequency catheter ablation in idiopathic ventricular tachycardia is reserved for patients who do not respond to medical therapy, with a success rate up to 80%; in patients with structural heart disease, the effectiveness of radiofrequency catheter ablation is lower, varying from 50% to 80%.[54,55]

### *Conclusion*

PVS still has many indications provided that it is appropriately implemented and interpreted: the ICD should not become a "second aspirin". The judicious use of non-invasive arrhythmia markers coupled with PVS is critical for assessing the risk of sudden cardiac death. PVS is still a useful and accurate tool for identifying patients at risk of sudden cardiac death in many cardiomyopathies, and ejection fraction is not sufficient alone to stratify patients at high risk of malignant VA. PVS yields a relatively high sensitivity in ischaemic heart disease, even when ejection fraction is low; in primary dilated cardiomyopathies, PVS has a good positive predictive value and a low negative predictive value. In addition, PVS has a good predictive value in other cardiac conditions, such as repaired tetralogy of Fallot, short-QT syndrome, sarcoidosis with cardiac involvement, and catecholaminergic polymorphic ventricular tachycardia.

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