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Who gets an invasive electrophysiological study for ventricular arrhythmias in 2000?

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Programmed electrical stimulation of the ventricle is often regarded as the 'gold standard' for risk stratification in patients susceptible to malignant ventricular arrhythmias and sudden cardiac death. However, data from the recent Multicenter UnSustained Tachycardia Trial (MUSTT) suggest that in patients with coronary artery disease, left ventricular ejection fraction <40% and asymptomatic nonsustained ventricular tachycardia (VT), negative programmed electrical stimulation largely fails to identify patients with a lower risk of death. This fact challenges the value of VT study in risk stratification. Although programmed ventricular stimulation remains an important diagnostic method in patients with syncope or documented wide QRS tachycardia, risk stratification cannot rely solely on the outcome of a VT study. Other risk stratifying variables may be more important – NYHA status, ejection fraction, heart rate variability – to determine the future role of prophylactic ICD therapy.

In spite of recent improvements in overall cardiovascular mortality, post-hospital mortality still remains significant (3% per year) in survivors of acute myocardial infarction (AMI). Importantly, there are subgroups with a significantly higher mortality risk. One-year mortality was 4% in patients with left ventricular ejection fraction (EF) >40%, compared to 45% in patients with EF <20% in the Multicenter Postinfarction Study that was conducted in the early 1980s, indicating that left ventricular function plays a major role in long-term survival.

The Canadian Assessment of Myocardial Infarction (CAMI) study showed that approximately 30% of late deaths in survivors of AMI are sudden and unexpected, and the risk of sudden death persists for years.[1] Sudden death is generally attributed to malignant ventricular tachyarrhythmias. Implantable defibrillators (ICDs) have proven to be effective in preventing death from recurrent ventricular tachycardia/ventricular fibrillation (VT/VF), and thus decrease both sudden death and total mortality in survivors of such arrhythmic events (secondary prevention). This has led to a shift towards earlier deployment of ICD therapy as a strategy of primary prevention. Primary prevention requires identification of patients at high risk of sudden death from VT/VF. Non-invasive risk stratification using EF, frequent ventricular premature beats (VPBs) on Holter monitoring, signal-averaged ECG, heart rate variability (HRV), baroreflex sensitivity, QT dispersion, and T-wave alternans each have a positive predictive value of approximately 40-50%.[2] Can programmed ventricular stimulation add to this risk assessment?

Principles of programmed ventricular stimulation

Initiation of any tachycardia requires a substrate for the arrhythmia (eg, peri-infarction zone) and a trigger (eg, ventricular premature beat), and is modified by many factors, most notably by the autonomic nervous system and ischemia. Programmed electrical stimulation provides the

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Table 1: Characteristic data on the prognostic value of programmed ventricular stimulation				
	Arrhythmic/ total mortality (%/year)	**Inducible patients**	**Positive predictive value**	**Comment**
All uncomplicated MI[5]	2.3%/4.5%	9%	30%	Only sustained monomorphic VT was considered specific
Post MI + noninvasive high risk[6]	5% (arrhythmic)	42%	65%	Misses ⅓ of events
Nonsustained VT (all)	0-13%	0-32%		Depends on underlying heart disease
Post MI+EF<40% +nonsustained VT[9]	5.2%/9.6%	35%	31%	Mortality of noninducible is similar to that of inducible
Aborted sudden death[11]	18%	50-60%		Negative VT study does not identify low risk group

trigger, which, in the presence of an appropriate substrate, will initiate tachycardia. There are two important limitations though:

• "aggressive" electrical stimulation may initiate polymorphic VT/VF even in a normal heart without any specific substrate for arrhythmia, and

• even appropriate triggers may not initiate tachycardia or reproducibility may be poor due to the effects of modifying factors despite the presence of a substrate.

Numerous studies over the last 20 years have largely defined the appropriate stimulation protocol and determined the "specific" and "non-specific" response to programmed electrical stimulation: the former has prognostic significance, while the latter lacks it. Programmed ventricular stimulation usually consists of stimulation at 2 right ventricular sites (apex and outflow tract) using 2 or 3 driving trains (600 ms, 400 ms and 350 ms), and up to 4 extrastimuli (the more extrastimuli used, the more sensitive but less specific the study) using coupling intervals longer than 180 ms to avoid non-specific VF induction.[3] It has been established in asymptomatic patients with uncomplicated AMI that only inducible slow (rate less than 260 BPM) sustained (lasting more than 10 seconds) monomorphic VT is predictive of subsequent events.[4] Thus, other inducible arrhythmias like nonsustained VT and polymorphic VT are generally regarded as non-specific responses, with the possible exception of patients with prehospital cardiac arrest.

However, the clinical usefulness of programmed ventricular stimulation still relies on the following assumptions:

• sudden death is due to VT/VF that occurs in context of no acute ischemia

• only patients who will spontaneously develop VT/VF have inducible VT

• VT is inducible any time (ie, at the time of VT study) in those patients

• a positive VT study is independent of left ventricular EF or other non-invasive risk factors

• targeted therapy will reduce sudden death and, consequently, total mortality.

Prognostic value of VT study in post-infarction patients without VT/VF

Characteristic data on the prognostic value of programmed ventricular stimulation in various clinical situations are summarized in Table 1.

In low risk patients with uncomplicated infarction, a positive VT study (ie, inducible VT) was the most powerful predictor of sudden death or VT/VF, but the positive predictive value was only 30% and the event rate was low.[5] An EF less than 40% improves the prognostic value of the VT study, and some data suggest that low EF alone may be a stronger predictor than a positive VT study.

To combine the predictive power of non-invasive risk stratification and the invasive VT study, a two-level risk stratification has been proposed. In this, noninvasive risk

stratification (EF, signal-averaged ECG, or Holter-based ventricular ectopy) is used to identify patients who will undergo VT study.[6] For example, in one study patients with at least 2 noninvasive risk factors (22% of all patients) underwent VT study, with inducible monomorphic VT in 42%. Arrhythmic events in follow-up were 65% in the inducible group, and 4% in the rest of the patients. The positive predictive value of the noninvasive risk stratification was 30%, and was improved to 65% by the VT study. However, only two-thirds of the arrhythmic events were predicted, indicating a fundamental paradox: the number of patients in the low-risk group is so high that the absolute number of events that occurs in this group is always higher than those that occur in the proportionally smaller high-risk group.

The challenge to VT study: Patients with spontaneous nonsustained VT

Nonsustained VT may indicate a risk of sudden death in patients with structural heart disease. Patients with a history of MI, low ejection fraction, and documented nonsustained VT had a 6% rate of sudden death at 2 years if VT was noninducible, a 11% rate of sudden death if the induced VT was suppressible by antiarrhythmic drugs, and a very high 50% rate of sudden death if the induced VT was not suppressible.[7]

MADIT

This observation led to the Multicenter Automatic Defibrillator Implantation Trial (MADIT), which demonstrated improved survival among 196 patients who were randomized to receive an implantable defibrillator as compared to patients receiving various antiarrhythmic drugs including Class I drugs (known to increase mortality from the CAST study) in patients with a history of MI, EF less than 35%, asymptomatic nonsustained VT, and inducible, but not intravenous procainamide suppressible, VT.[8] Unfortunately there was no registry data, so we know little about selection biases to study entry, as well as the survival data of the patients with inducible, but suppressible VT or patients with no inducible VT. Therefore, there is no control group in the MADIT study that would confirm the value of VT study in identifying a high-risk subgroup of patients.

MUSTT

The Multicenter Unsustained Tachycardia Trial (MUSTT) enrolled patients similar to MADIT: patients with coronary artery disease, EF <40%, and asymptomatic nonsustained VT.[9] The primary endpoint was to compare programmed ventricular stimulation guided therapy (which ended up being ICD therapy in 65% of patients) to no antiarrhythmic therapy. To enter MUSTT, all patients had to have inducible VT, the rest were entered into a registry. This study provided a reasonable good control group to assess the value of VT study: noninducible registry patients (1435 patients) were compared to inducible randomized not-to-be-treated patients (353 patients). The 5-year cardiac arrest and arrhythmia mortality was as bad in the noninducible group as in the inducible but not-treated group (26% vs 32%), with no difference in the 5-year total mortality (48% vs 48%). The lack of a difference in outcome between inducible and noninducible patients may be explained in many ways:

- VT study may have no value in identifying higher risk patients in an already preselected high risk group,
- the inducibility criteria were not specific enough to identify the high risk patients, or
- inducible sustained polymorphic VT or nonsustained VT might also have prognostic significance and thus should not be regarded as nonspecific responses.

A recent subgroup analysis of MUSTT supports the last possibility: induction of sustained polymorphic VT using 3 extrastimuli may be more meaningful than previously thought.[10] For now, however, inability to induce monomorphic VT in the high-risk MUSTT population has little value.

The current concern over the prognostic value of programmed ventricular stimulation is demonstrated in the design of ongoing and planned trials on sudden death prevention in high-risk patients. Some trials will use programmed ventricular stimulation in risk stratification, some intend to capture data for a retrospective evaluation of the value of VT study, while others will utilize only noninvasive risk stratification such as impaired left ventricular function or heart rate variability. The final expression of pessimism attached to risk stratification are those trials that will cast the widest net with entry based on EF and NYHA class only. Nonetheless, many feel that even if these trials are positive, there may be a health economic driven need to use risk stratification to identify patients who may benefit most.

Secondary prevention in patients with documented sustained VT or aborted sudden death

In patients with aborted sudden death in the context of acute MI or any reversible cause, sustained VT

Table 2: Indications for VT study

Diagnosis

- Documented tachycardia: wide QRS tachycardia with unknown mechanism
- No documented tachycardia but suspected on clinical grounds: syncope in structural heart disease

Treatment

- Curative therapy contemplated: slow VT in scarred heart, IDC macro-reentry, pre-operative VT surgery
- Testing before/during follow-up ICD: only in special circumstances

Risk stratification

- Documented VT/VF with reversible cause or in unclear clinical settings or patient has undergone revascularization since the arrhythmic event
- Post-infarction patients with an ejection fraction < 35% and documented nonsustained VT: if the perceived risk of sudden death by the complete clinical picture is high and if there is no clinical trial to enter.*

* Note that MUSTT criteria have been proposed as a Grade B (Level 2 evidence) ICD indication by the Canadian Cardiovascular Society primary consensus panel on the therapy and prevention of ventricular arrhythmias.

(monomorphic or polymorphic) is only inducible in approximately 50-60%. Both the Canadian Implantable Defibrillator Study (CIDS) and the Antiarrhythmics versus Implantable Defibrillators (AVID) trial clearly demonstrated that these patients are at high risk of sudden death and should be treated with implantable defibrillators.[11] Note that in the CIDS trial, entry was based on syncope as a surrogate of VT/VF if the patient had an EF <40% and inducible VT.

The risk of recurrent VT/VF is less defined in patients with documented VT/VF that occurs in the context of ischemia, metabolic imbalance, surgery, or any other significant reversible circumstance. Data on the prognostic value of a VT study in such cases is sparse and based on case reports and small studies, therefore no conclusion can be made. Risk stratification should be based on the whole clinical picture, including the outcome of the VT study.

There are controversial data regarding the effect of revascularization on future risk of sudden death following documented VT/VF. In one small series prior to the defibrillator era, 50 patients who underwent bypass surgery after aborted sudden death, had a low 5-year mortality (12%), and induction of VF was prevented by revascularization in patients who had VF that was inducible before surgery.[12] Two other studies using either population-based registries or ICD shock events, similarly demonstrated the benefit of revascularization as an adjunct to secondary prevention of sudden death. By inference from a primary prevention trial (CABG-Patch), revascularization by itself in patients perceived to be at high risk of sudden death (EF <40% and positive signal-averaged ECG) obviated any potential benefit of prophylactic ICD implantation. In contrast, in another study of 58 patients with VF arrest who received ICD at the time of the bypass surgery, 70% of patients received appropriate shocks during a 4-year follow-up.[13] Overall, we base our risk stratification on the whole clinical context, including the outcome of a VT study following revascularization.

Role of VT study in non-ischemic cardiomyopathy

In patients with dilated cardiomyopathy, up to 30% of the monomorphic VTs are due to bundle branch reentry that may be eliminated by radiofrequency catheter ablation after careful diagnostic study. Programmed ventricular stimulation has generally failed to identify patients at high risk of future VT/VF. In the largest pooled database of 288 patients with dilated cardiomyopathy, VT study failed to identify 75% of the patients who died suddenly.[14]

Some of the current trials that include patients with dilated cardiomyopathy and low ejection fraction may help to determine the appropriate risk stratification approach in those patients.

A recent retrospective multicenter ICD trial involving patients with hypertrophic cardiomyopathy and history of cardiac arrest/sustained VT indicated that the majority of these high-risk patients have inducible VT/VF (87%), but non-inducibility does not mean lower risk as 33% of the non-inducible patients received appropriate therapy in contrast to the 24% of inducible patients.[15]

Summary and conclusion

Programmed ventricular stimulation, especially when dichotomized as inducible sustained monomorphic VT and noninducible, should not be regarded as the "gold standard" for risk stratification of sudden cardiac death. Revision of the specific and nonspecific outcomes of VT study may be necessary to improve its prognostic value. Current trials will help to determine its role in risk stratification compared to the noninvasive risk assessment which is more feasible and more widely accessible.

As summarized in Table 2, programmed ventricular stimulation is still a very useful diagnostic method in patients with documented wide QRS tachycardia of unknown mechanism and in patients with syncope or palpitations and structural heart disease. It is also an essential tool to initiate ventricular tachycardia when definitive therapy (radiofrequency catheter ablation or surgery) is attempted. For risk stratification, we do not systematically use it in patients with asymptomatic nonsustained VT because of the lack of proof of the value of VT study in identifying patients at a higher risk of future arrhythmic death. On the other hand, the outcome of a VT study may play a significant role in the clinical decision making in cases of documented VT/VF that occurred in context of a potentially reversible cause or the clinical circumstances were unclear.

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Abstracts of Interest

Are there subgroups of patients at high risk for sudden death and cardiac arrest without inducible sustained monomorphic ventricular tachycardia – results from Multicenter Unsustained Tachycardia Trial (MUSTT)

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MUSTT showed that in patients with coronary artery disease , LVEF ≤0.40, and spontaneous nonsustained ventricular tachycardia (VT-NS), induction (IND) of sustained VT (VT-S) (Grl) at electrophysiologic study without subsequent antiarrhythmic therapy significantly increased the risk for sudden death or cardiac arrest (SD/CA). Patients without induced monomorphic VT-S (Grl) are a heterogeneous group, and the purpose of this study was to define subgroups at higher risk for SD/CA. In 1,396 Grl patients, clinical characteristics and type of VT IND were analyzed, and results compared with Grl pts. Risk of SD/CA was less ($p < 0.04$) without VT IND or IND of monomorphic VT-NS. Of note, whereas IND of polymorphic VT-NS had least ($p=0.001$) risk (0.91 SD/CA 2-y event rate), IND of polymorphic VT-S with 3 extrastimuli (N=205) was not different from Grl SD/CA events. Several clinical variables were associated with a statistically significant difference in SD/CA events. There was an increased risk for SD/CA with NYHA II or III versus I (Hazard ratio = 2.22): LVEF <0.30 vs ≥0.30 (HR=2.17); spontaneous VT-NS ≥6 vs <6 beats (HR=1.59); combination of VT-NS ≥6 beats and VT-NS cycle length ≤345 ms (HR=1.51); and positive vs negative signal averaged ECG (HR=1.41). We conclude that (1) noninducibility of monomorphic VT-S alone is not a good descriminator of future SD/CA events; (2) specific high-risk subgroups can be identified; and (3) induction of polymorphic VT-S with 3 extrastimuli may be more meaningful than previously thought.

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Differences in baseline characteristics and outcomes in patients with induced sustained monomorphic versus polymorphic ventricular tachycardia

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The significance of induced sustained polymorphic VT (PMVT) at EP study is unclear. The purpose of this study was to analyze baseline characteristics and outcomes from 1,009 pts with CAD, LVEF ≤0.40, and nonsustained VT (VT-NS) who had induction of sustained PMVT (n=285) or monomorphic VT (MVT, n=724) at EPS. Differences in clinical characteristics were (Table): Time from MI was a median of 6 and 25 mos for PMVT induced with 2 (n=74) and 3 (n=210) extrastimuli, respectively. For all randomized pts, 2-year total mortality rate was higher in MVT vs PMVT pts (26.3% vs 15.9%, $p=0.011$), but the rate of arrhythmic death or cardiac arrest was similar (15.1% vs 14.5%, $p=0.396$).

Conclusion: Pts with induced PMVT vs MVT are younger, have had a more recent MI, and have a better overall survival rate. It is possible that myocardial remodeling over time yields more stable reentrant circuits.

	MVT	PMVT	P-value
Av duration VT-NS (beats)	6.0	4.0	0.015
LVEF (%)	29	30	0.039
Time from MI (months)	41	19	0.031
Age (years)	67	64	0.020
SAECG (abnormal)	66	51	<0.001

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