Bradycardia Pacing-Induced Short-Long-Short Sequences at the Onset of Ventricular Tachyarrhythmias

A Possible Mechanism of Proarrhythmia?

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Objectives

The purpose of this study was to characterize interactions between normal pacing system operation and the initiating sequence of ventricular tachycardia (VT)/ventricular fibrillation (VF).

Methods

Initiating sequences of 1,356 VT/VF episodes in the PainFree Rx II (n = 634) and EnTrust Trial (n = 421) were analyzed with stored electrograms and by pacing mode (DDD/R, VVI/R, and Managed Ventricular Pacing [MVP]). Interactions between pacing and VT/VF initiation were classified as: non-pacing associated, pacing associated, pacing permitted, and pacing facilitated.

Results

Non-pacing associated (no pacing, no S-L-S) and pacing associated (ventricular pacing without S-L-S) onset accounted for 44.0% and 29.8% of all VT/VF, respectively. Pacing permitted (S-L-S sequences without ventricular pacing) episodes accounted for 6.4% (DDD/R), 20.0% (MVP), and 25.6% (VVI/R) of 1,356 VT/VF episodes. Pacing facilitated onset (S-L-S sequences actively facilitated by ventricular pacing including the terminal beat after a pause) accounted for 8.2% (MVP), 9.4% (VVI/R), and 14.8% (DDD/R) of 1,356 VT/VF episodes. Pacing facilitated S-L-S VT/VF occurred in 2.6% (MVP), 3.3% (VVI/R), and 5.2% (DDD/R) of patients with episodes and was the sole initiating sequence in approximately 1% of patients. Pause durations during pacing facilitated S-L-S differed between modes (DDD/R 793 ± 172 ms vs. MVP 865 ± 278 ms vs. VVI/R 1180 ± 414 ms, p = 0.002). The majority of these episodes were monomorphic VT.

Conclusions

Ventricular tachycardia/VF in some implantable cardioverter-defibrillator patients might be initiated by S-L-S sequences that are actively facilitated by bradycardia pacing operation and might constitute an important mechanism of ventricular proarrhythmia. (J Am Coll Cardiol 2007;50:614–22) © 2007 by the American College of Cardiology Foundation

Abrupt changes in ventricular cycle lengths (CLs) or short-long-short (S-L-S) sequences might precede initiation of ventricular tachycardia (VT) and ventricular fibrillation (VF). The S-L-S sequences might be passively permitted or actively facilitated by pacing. During pacing facilitated S-L-S, both ventricular intervals and activation sequence are altered suddenly. The purpose of this study was to systematically classify the onset patterns of spontaneous VT/VF among implantable cardioverter-defibrillator (ICD) patients in order to characterize interactions between normal pacing system operation and the initiating sequence of VT/VF.

Methods

Study population. The study population was derived from the 634-patient PainFREE Rx II trial and the 421-patient EnTrust Clinical trial. Ventricular leads were placed at the right ventricular apex (RVA). Follow-up duration was 11.3 ± 5.0 months and 5.3 ± 3.9 months, respectively.
Tachycardia detection and therapy programming. Detection programming was standardized. Detection in the VF zone required that 18 of 24 R-R intervals had cycle length (CL) <320 ms. A VT zone with CL 320 to ≥360 ms was required in PainFREE Rx II, whereas a VT zone with CL 400 ms or clinical VT CL + ≥30 ms, whichever was greater, was required in EnTrust. Both studies specified loss of AV conduction and switches to DDD/R mode during AV block (1).

Pacing mode. Dual-chamber ICDs were used in 75% and 100% of patients in PainFREE Rx II and EnTrust, respectively. Pacing mode was Managed Ventricular Pacing (MVP) in 92% of patients in EnTrust. Managed Ventricular Pacing is an enhanced AAI/R mode that continuously monitors ventricular activity for loss of atrioventricular (AV) conduction and switches to DDD/R mode during AV block (1).

Selection of patients and ventricular episodes for analysis. Only patients with ≥1 spontaneous ventricular episode that satisfied VT/VF detection criteria and with corresponding EGMs and sufficient beats (generally ≥5) with CL ≤detection interval before VT/VF onset were included. If EGM pre-storage revealed VT with CL >detection interval (i.e., below detection rate cut-off), insufficient beats before onset with CL ≤detection interval or therapy (indicating an ongoing episode), the episode was excluded.

Rhythm classification and definitions. Site investigators reviewed and classified all VT/VF episodes. A review committee also reviewed each episode in PainFREE Rx II. All ventricular episodes were subjected to a third review (M.O.S., L.R., T.S.). Disagreement regarding ventricular origin of tachycardia was settled by majority rule.

The EGMs, Marker Channel annotations, and ventricular (and atrial, if available) intervals were used to characterize the initiating sequences. Monomorphic VT (MMVT) was defined as a single constant EGM morphology be-

![Image with labels and annotations](VVI/R)

For pacing facilitated short-long-short (S-L-S), sinus rhythm is interrupted by a single ventricular premature depolarization (VPD) (coupling interval 700 ms, asterisk) ("short"). A 1,500-ms pause (bracket) ("long") is terminated by a single ventricular paced beat (VP) at the lower rate limit (40 beats/min). A VPD (coupling interval 440 ms) ("short") after the VP anticipates ventricular tachycardia (VT) that degenerated to ventricular fibrillation (VF) (not shown).

**Abbreviations and Acronyms**

- **AP** = atrial pace
- **APD** = atrial premature depolarization
- **AV** = atrioventricular
- **CL** = cycle length
- **EGM** = electrogram
- **ICD** = implantable cardioverter-defibrillator
- **MMVT** = monomorphic ventricular tachycardia
- **MVP** = Managed Ventricular Pacing
- **RVA** = right ventricular apical
- **S-L-S** = short-long-short
- **VF** = ventricular fibrillation
- **VP** = ventricular paced beat
- **VPD** = ventricular premature depolarization
- **VT** = ventricular tachycardia
fore satisfying detection criteria; VF was defined as a ventricular rhythm with median CL <240 ms before detection.

Ventricular arrhythmia onset pattern classification. Interactions between pacing and VT/VF initiation were classified into 4 onset pattern categories: 1) non-pacing associated, 2) pacing associated, 3) pacing permitted, and 4) pacing facilitated (Figs. 1, 2, and 3).

DEFINITIONS OF VT/VF ONSET PATTERNS: 1) NON-PACING ASSOCIATED, AND 2) PACING ASSOCIATED. The VT/VF episodes initiated by ventricular premature depolarizations (VPDs) unaccompanied by pauses were classified according to: 1) absence (non-pacing associated), or 2) presence (pacing associated) of VPs within 5 cycles before initiation. Late-coupled VPDs had prematurity index of the initiating beat of VT/VF \( \geq 0.5 \) (RR\(_0\)/RR\(_{-5}\) \( \geq 0.5 \)) (2). Early-coupled VPDs had prematurity index \(<0.5\). For late- and early-coupled initiating sequences, the VPD had a different morphology from the ensuing MMVT. “Sudden onset” VT described the situation where the initiating late-coupled VPD was morphologically identical to the ensuing MMVT; fusion with the last non-VT beat was permitted only if the first R-R interval was identical to preceding non-VT intervals.

DEFINITIONS OF VT/VF ONSET PATTERNS: 3) PACING PERMITTED, AND 4) PACING FACILITATED. The VT/VF episodes initiated by S-L-S sequences (“pauses”) were classified as: 3) pacing permitted (passively allowing longer pauses depending upon mode and lower rate), or 4) pacing facilitated (actively initiating and/or terminating pauses prematurely with single VPs). If VPs did not participate in S-L-S generation, the episode was designated as pacing permitted. If VPs participated in the S-L-S including the pause-terminating beat, the episode was designated as pacing facilitated. Episodes were categorized as S-L-S if the pauses were longer than the basic CL by \( \geq 40 \) ms (3).

Statistical methods. Descriptive statistics are presented as means ± SDs for continuous variables or percentages for discrete variables. Differences between means for PainFREE Rx II and EnTrust were assessed with unpaired t tests. For discrete variables, distributions between studies were compared with chi-square tests. Repeated measures techniques were used to analyze episode data to account for: 1) variable numbers of episodes among patients, and 2) correlations among episodes within patients. Generalized estimating equation methods were used in the analysis of
Results

Baseline characteristics. The study population consisted of typical ICD patients (Table 1). There were fewer primary prevention patients in PainFREE Rx II, which was completed before adoption of expanded indications.

Spontaneous VT/VF. One thousand three hundred fifty-six spontaneous ventricular episodes with pre-storage EGMs were available (1,002 episodes from 139 patients in PainFREE Rx II and 354 episodes from 65 patients in EnTrust). Ventricular tachycardia detection programming compliance was 92.2% in PainFREE and 93.3% in EnTrust (p = 0.57). Episodes in MVP patients occurring in DDD/R mode were excluded from the MVP episode cohort. VT/VF onset patterns: 1) non-pacing associated, and 2) pacing associated. Non-pacing associated and pacing associated onset accounted for 44.0% and 29.8% of all VT/VF episodes, respectively (Table 2). Of these, 729/1,000 (72.9%) episodes were sudden onset, 260/1,000 (26.0%) were late-coupled VPD onset, and 11/1,000 (1.1%) were early-coupled VPD onset.

VT/VF onset patterns: 3) pacing permitted S-L-S, and 4) pacing facilitated S-L-S. The S-L-S sequences were early-coupled VPD (390 ms) (“short”) anticipates VT/VF onset. Abbreviations as in Figure 1.

episode type associated with onset patterns. Random effects regression models were used to compare pause durations between modes. Patients with ≥1 episode were included in the repeated measures analyses. Owing to differences in the study populations, comparisons of results among patient groups were adjusted for covariates with significant differences among the groups. All statistical analyses were conducted with software from SAS Institute, Inc. (Cary, North Carolina). Statistical tests with p values <0.05 were considered statistically significant.

Figure 3 Managed Ventricular Pacing

For pacing facilitated S-L-S, a VPD (600-ms interval, asterisk) (“short”) occurs almost simultaneously with an atrial pace (AP) (800-ms interval). The VPD is marked as a sensed event but, because it falls in the 80-ms cross-talk window, is not considered a true ventricular event. The next AP (800 ms) fulfills the criteria for an AA interval without an intervening ventricular sense (VS) event, and a single VP is delivered (“long”). The pause (bracket) is only 830 ms, because of rate modulation. An early-coupled VPD (390 ms) (“short”) anticipates VF onset. Abbreviations as in Figure 1.
at high frequency in DDD/R. Pause duration in pacing permitted S-L-S episodes was 816 ± 1100 ms (range 380 to 1400 ms) across modes, 762 ± 190 ms for DDD/R (range 380 to 1020 ms), 824 ± 223 ms for VVI/R (range 390 to 1370 ms), and 828 ± 165 ms for MVP (range 510 to 1400 ms). Adjusting for differences in patient characteristics, pause durations for DDD/R were significantly less than VVI/R (p < 0.001) but not MVP (p = 0.156).

VT/VF ONSET PATTERN 4: PACING FACILITATED S-L-S. Pacing facilitated S-L-S accounted for 8.2%, 9.4%, and 14.8% of all VT/VF episodes during MVP, VVI/R, and DDD/R, respectively.

Although amiodarone and sotalol might be associated with pause-dependent VT/VF, no significant differences in the percentage of patients with episodes or proportion of pacing facilitated S-L-S VT/VF were observed for either drug.
VT/VF onset pattern 4: pacing facilitated S-L-S by pacing mode. Characteristic patterns of pacing system participation in onset patterns and specifically during pacing facilitated S-L-S VT/VF were observed.

VVI/R. The first short cycle was most often due to single VPDs (92.5%) (Fig. 1). Ventricular CL variation due to sinus arrhythmia or atrial fibrillation (AF) accounted for 7.5% of first short cycles. A single VP always terminated the long cycle.

DDD/R. The first short cycle was most commonly due to VPDs (77.4%); AF and single atrial premature depolarizations (APDs) accounted for 22.6% (Fig. 2). The latter situation is unique to upper rate tracking behavior in DDD/R where APDs triggered VPs. The long sequence was similar to VVI/R but was terminated by an atrial-synchronous VP.

MVP. The first short cycle was always due to VPDs (Fig. 3). Long cycles followed VPDs that were incorrectly classified as electrical crosstalk, because they occurred coincident with an atrial pace (AP) (92%) or owing to VPDs with subsequent AV conduction failure (8%).

PAUSE DURATIONS DURING PACING FACILITATED S-L-S BY PACING MODE. Mean pause duration during pacing facilitated S-L-S VT/VF was 911 ± 322 ms (500 to 1,760 ms) (Fig. 4). Pause duration was different among modes (VVI/R 1,180 ± 414 ms vs. MVP 865 ± 278 ms vs. DDD/R 793 ± 172 ms; p = 0.002). Pause duration was shorter for DDD/R vs. VVI/R (p < 0.001) and for MVP vs. VVI/R (p = 0.033) but not for DDD/R vs. MVP (p = 0.607).

Differences in pause duration were primarily due to lower rate programming. For VVI/R, the lower rate was nominally 40 beats/min, whereas for DDD/R and MVP lower rates were 60 beats/min. Shorter pauses were seen during rate modulation. Because MVP permits single non-conducted atrial events, the maximum pause duration is twice the programmed lower rate interval. However, because S-L-S sequences during MVP were nearly always initiated by VPDs coincident with an AP event rather than a non-conducted atrial event, the resulting pauses were typically near the lower rate.

Incidence of pacing facilitated S-L-S and contribution to total VT/VF burden. Pacing facilitated S-L-S VT/VF occurred in 3% to 5% of all patients and was the only form of VT/VF observed in approximately 1% to 2% of patients in any mode (Table 3). The percentage of patients with pacing facilitated S-L-S VT/VF might be underestimated, owing to censuring of episodes that did not qualify.

Because approximately 80% of patients did not have a VT/VF episode, the percentage of pacing facilitated S-L-S that occurred in patients with VT/VF episodes was higher (Table 4). Approximately 11% to 28% of patients with episodes had some pacing facilitated S-L-S VT/VF. Likewise, 4% to 10% of patients with episodes had pacing facilitated S-L-S as the sole onset sequence preceding VT/VF.

Characteristics of pacing facilitated S-L-S onset pattern VT/VF. The vast majority of pacing facilitated S-L-S episodes were MMVT, and CLs were similar to MMVT with non-pacing facilitated onset patterns (Table 5). The incidence of VF trended higher during pacing facilitated S-L-S but was not significant (p = 0.125).

Discussion

The main findings of this study are: 1) pacing facilitated S-L-S VT/VF accounted for 8% to 15% of all VT/VF, 2) pacing facilitated S-L-S VT/VF was observed in 11% to 28% patients with VT/VF, 3) pacing facilitated S-L-S
VT/VF was the only onset sequence in approximately 4% to 10% of patients with VT/VF, and 4) pacing facilitated S-L-S VT/VF is common to all pacing modes but is invoked in different ways specific to mode.

This study emphasizes that S-L-S sequences are an important onset pattern for VT/VF. Although VPDs initiated approximately 70% of all VT/VF, approximately 30% were initiated by S-L-S sequences either passively permitted or actively facilitated by pacing. Most pacing facilitated S-L-S episodes were MMVT. Most patients had coronary disease, and scar-related re-entry is the most common mechanism of VT in this setting. This implies that the S-L-S sequence satisfies the classic conditions (unidirectional conduction delay and block) for initiation of re-entry. The pause might facilitate block in 1 limb of the circuit while the terminal VP propagates through the opposing limb with sufficient delay to allow the previously blocked limb to recover excitability. This is an intriguing observation, because S-L-S sequences are characteristically associated with the torsades de pointes form of polymorphic VT (3,4).

Our results pose several competing implications. Pause suppression to prevent VT/VF is a tempting target for pacing techniques. Pacing modes or lower rate programming that permit bradycardia might passively facilitate pause dependent VT/VF. Simple overdrive pacing and dedicated pause suppression techniques might be useful in selected patients (5,6), but active ventricular pacing-based pause suppression has not been shown to reduce VT/VF (7). This approach likely failed owing to: 1) overemphasis on pause duration, and 2) lack of awareness of the proarrhythmic effect of critically timed VPs (VPD mimicry). In 1 small study of highly selected patients, suppression of pauses by increasing the pacing rate in VVI/R did not prevent pacing-facilitated VT/VF in any patient, whereas deactivation of pacing abolished the phenomenon despite increased duration of pauses (8). Our data supports this observation, because in all modes the minimum pause duration during pacing-facilitated S-L-S VT/VF was 500 ms and relatively small numbers of episodes occurred after pauses >1,000 ms.

Although it is intuitive that shorter pauses in DDD/R might be less proarrhythmic than longer pauses in other modes or at lower rates, this logic ignores the evidence that changes in refractory periods of the His-Purkinje system and ventricular muscle occur very rapidly in response to even slight oscillations in ventricular CLs (9). Likewise, the mean pause duration preceding onset of torsade de pointes in long QT syndrome was approximately 1,000 ms, and the difference between the basic ventricular CL and the pause duration was only approximately 40 to 200 ms in most patients (3). The S-L-S sequences during DDD/R at or near the typical upper rate limit (500 to 600 ms) closely approximate initiating sequences in pacing models where pauses of only 600 ms bracketed by timed ventricular stimuli were sufficient to induce MMVT due to macroreentry involving the His-Purkinje system (10).

Our data imply that the approach to overcoming pacing permitted pauses must consider the reciprocal possibility of pacing facilitated S-L-S VT/VF with any technique that introduces critically timed VPs.

A causal relationship between isolated VPs and VT/VF was established in a small study where 26% of single-chamber ICD patients had pacing facilitated VT/VF (8). The present study extends this concept amongst a much larger and more diverse cohort and demonstrates that critically timed delivery of isolated VPs in any pacing mode might actively facilitate S-L-S VT/VF. The common pattern among all modes is an

| Table 3 | Occurrence of Pacing Facilitated S-L-S VT/VF Within the Study Population |
|-----------------|-----------------|-----------------|
| Pacing Mode     | MVP (AAIR+)     | DDD/R           | VVI/R           |
| (n = 386 Patients) | (n = 483 Patients) | (n = 184 Patients) |
| Any pacing facilitated S-L-S VT/VF observed | | |
| Patients with ≤1 episode, n (%) | 10 (2.6) | 25 (5.2) | 6 (3.3) |
| Mean # episodes/patient | 1.3 ± 0.5 | 3.4 ± 3.4 | 6.7 ± 5.9 |
| Range of episodes/patient | 1-2 | 1-14 | 1-15 |
| Only pacing facilitated S-L-S VT/VF observed | | |
| Patients with only pacing facilitated S-L-S VT/VF, n (%) | 6 (1.6) | 6 (1.2) | 2 (1.1) |
| Mean # episodes/patient | 1.0 | 1.2 ± 0.4 | 2.0 ± 1.4 |
| Range of episodes/patient | 1-1 | 1-2 | 1-3 |

Abbreviations as in Tables 1 and 2.

| Table 4 | Relative Occurrence of Pacing Facilitated S-L-S Among Patients With Any Spontaneous VT/VF |
|-----------------|-----------------|-----------------|
| Pacing Mode     | MVP (AAIR+)     | DDD/R           | VVI/R           |
| (n = 63 Patients) | (n = 88 Patients) | (n = 53 Patients) |
| Patients with only non-pacing facilitated VT/VF, n (%) | 53 (84.1) | 63 (71.6) | 47 (88.7) |
| Patients with only pacing facilitated S-L-S VT/VF, n (%) | 6 (9.5) | 6 (6.8) | 2 (3.8) |
| Patients with pacing facilitated S-L-S VT/VF and non-pacing facilitated VT/VF, n (%) | 4 (6.3) | 19 (21.6) | 4 (7.5) |

Abbreviations as in Tables 1 and 2.
apart change in ventricular CLs and activation sequence that is initiated and terminated by VPDs and/or VPD-surrogates in the form of single VPs. These sudden oscillations replicate ventricular pacing models for the sequential occurrence of extrasystolic beats that increase dispersion of refractoriness and favor re-entry (9,11). The VVI/R mode provides the simplest model for pacing facilitated S-L-S VT/VF, because it requires only a single VPD and pause. The interaction between pacing system operation and S-L-S sequences is more complex in DDD/R. Although single VPDs accounted for the majority of S-L-S initiations in DDD/R, nearly 25% were due to atrial tracking behavior. Pacing facilitated S-L-S VT/VF during MVP requires the simultaneous occurrence of 2 unrelated events—a critically timed VPD coincident with an AP that triggers the S-L-S and is terminated with an unnecessary VP or transient loss of AV conduction after a VPD.

Our study also identifies an important distinction between the mere presence of VPs and the occurrence of pacing facilitated S-L-S VT/VF. The incidence of pacing facilitated S-L-S VT/VF as the only observed VT/VF onset sequence was very low (approximately 1%) overall. However, the proportionate contribution of pacing facilitated S-L-S VT/VF to all onset sequences among those patients with VT/VF episodes was greater. Therefore, there must be other requisites for the pacing facilitated S-L-S VT/VF phenomenon, because the incidence is obviously much lower than the frequency of triggers (VPDs, isolated VPs) causing S-L-S sequences (1). Patients who had pacing facilitated S-L-S VT/VF also often had spontaneous VT/VF with other onset patterns. This suggests that these patients have multiple triggering mechanisms because of a highly conducive substrate for reentry.

Overcoming pacing facilitated S-L-S VT/VF could be difficult. Switching modes might not eliminate the problem, because it can occur in any mode. Deactivation of ventricular pacing might be effective in some patients (8) but might be clinically undesirable. Conversely, increasing the lower rate in VVI/R might be ineffective (8), and higher frequency RVA pacing is associated with increased risks of heart failure (12). The S-L-S behavior is difficult to abolish in DDD/R, because it is inherent to dual chamber timing rules. The addition of ventricular-based pause suppression to DDD/R is not reliably effective, and the adverse effects of RVA pacing might be magnified. Managed Ventricular Pacing minimizes ventricular pacing; however, appropriate single VPs for transient loss of AV conduction are still possible.

**Clinical implications.** Pacing facilitated S-L-S VT/VF might occur despite a very low frequency of single VPs. Therefore, pacing facilitated S-L-S VT/VF might occur even in patients who do not actively require bradycardia support. Our study does not identify patients who might be susceptible to pacing facilitated S-L-S VT/VF, and this might only be possible retrospectively.

**Study limitations.** This is a retrospective analysis. Results are presented in a descriptive manner, and comparisons of the absolute incidence of pacing facilitated S-L-S VT/VF across trials and pacing modes is potentially misleading. We cannot definitively conclude that ventricular pacing sequences were the explicit cause of VT/VF or comment on the possibility of site-specific effects, because all pacing was delivered from the RVA. However, this analysis provides a framework and definitions for further study.

**Conclusions**

Ventricular tachycardia/VF in ICD patients is initiated by S-L-S sequences that might be facilitated by normal pacemaker operation and might constitute an important mechanism of ventricular proarrhythmia. Enhancements to bradycardia pacing operation to reduce the possibility of ventricular proarrhythmia merit further investigation.

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