Inducing PVCs and VTs during EP study: Tips and Pitfalls

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1. Programmed ventricular stimulation (PVS)

- **Purpose**
  - To evaluate the inducibility of VT
  - To characterize the VT and assist in the choice of therapy
  - For the purposes of catheter mapping and ablation
  - To evaluate the efficacy of treatment

(J Am Coll Cardiol 1993;22:1711–7)

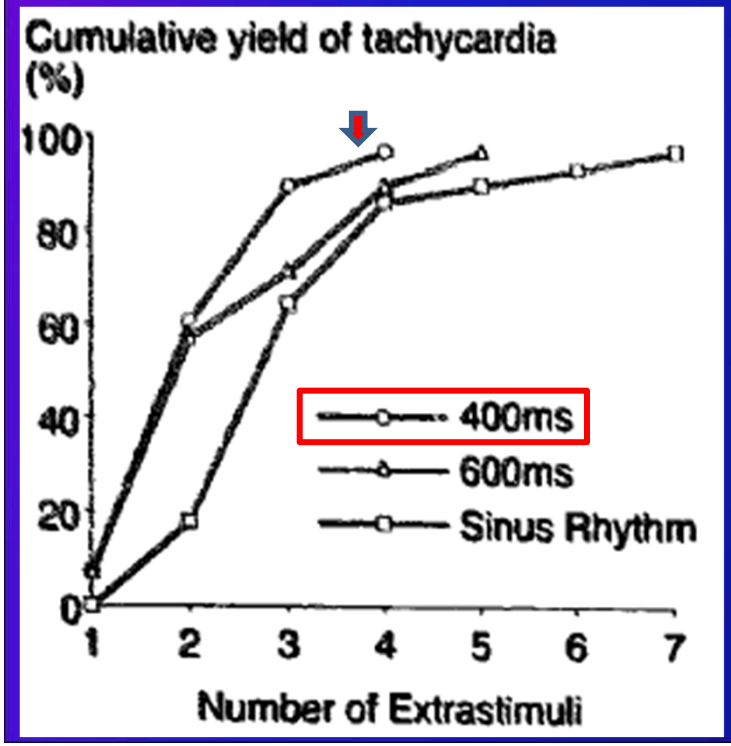
Four main components of PVS

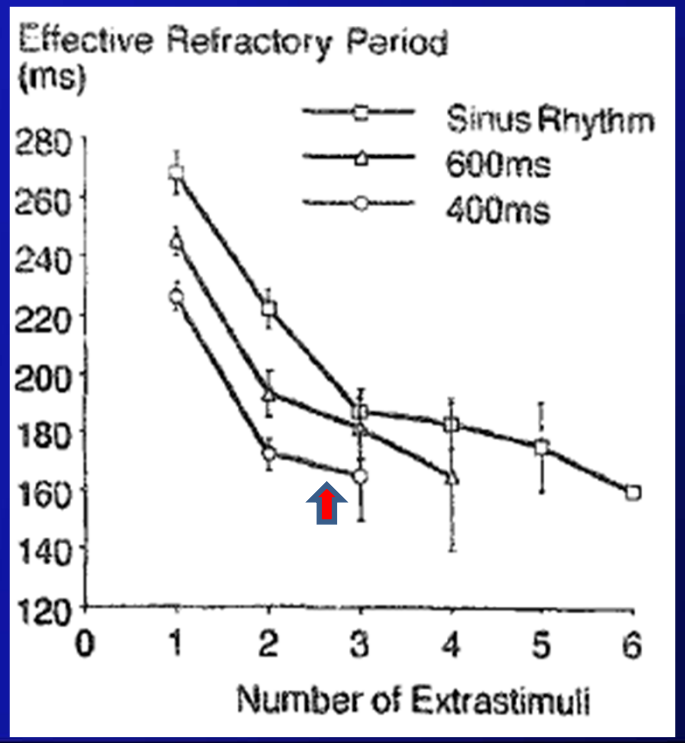
- **Site of stimulation:** RV apex, RVOT, and LV
- **Current of stimulation**
- **Basic cycle length (BCL):** 8-beat pacing drive train (S1) (CL 600 ms and 400 ms)
  - Ventricular burst pacing
  - Incremental ventricular pacing
- **Number of extrastimuli** (main mechanism: reentrant)
  - Single, Double, Triple (S2/S3/S4)
  - Multiple extrastimuli pacing: short-long-short (SLS) sequences (may facilitate induction of bundle branch reentry)

(J Am Coll Cardiol 1993;22:1711–7)

BCL and No. of extrastimuli

- BCL 400 ms required fewer extrastimuli (2.4±0.7) to induce VT/VF than did 600 ms (2.7±1.1, p=0.014) or sinus rhythm (3.4±1.2, p <0.001) .
- No significant difference in the CL of the induced VT, incidence of induced VF or requirement for DC countershock .
- **Ventricular pacing (BCL 400 ms) with up to at least four extrastimuli** as the standard stimulation protocol for induction of VT.





(J Am Coll Cardiol 1993;22:1711–7)

Triple extrastimuli vs. LV stimulation

Stimulation protocols A and B

Protocol A

(1) Right ventricular apex: OD, S_2, S_2S_3, $S_2S_3S_4$

(2) Right ventricular outflow/septum: OD, S_2, S_2S_3, $S_2S_3S_4$

(3) Left ventricle: OD, S_2, S_2S_3, $S_2S_3S_4$

Protocol B

(1) Right ventricular apex: OD, S_2, S_2S_3

(2) Right ventricular outflow/septum: OD, S_2, S_2S_3

(3) Left ventricle: OD, S_2, S_2S_3

(4) Right ventricular apex: $S_2S_3S_4$

(5) Right ventricular outflow/septum: $S_2S_3S_4$

(6) Left ventricle: $S_2S_3S_4$

OD = overdrive pacing.

indicate that triple extrastimuli are more effective in inducing clinical ventricular tachycardia than is left ventricular stimulation.

advantage is offset by a tendency to increase the yield of nonclinical ventricular tachycardia. If the end point

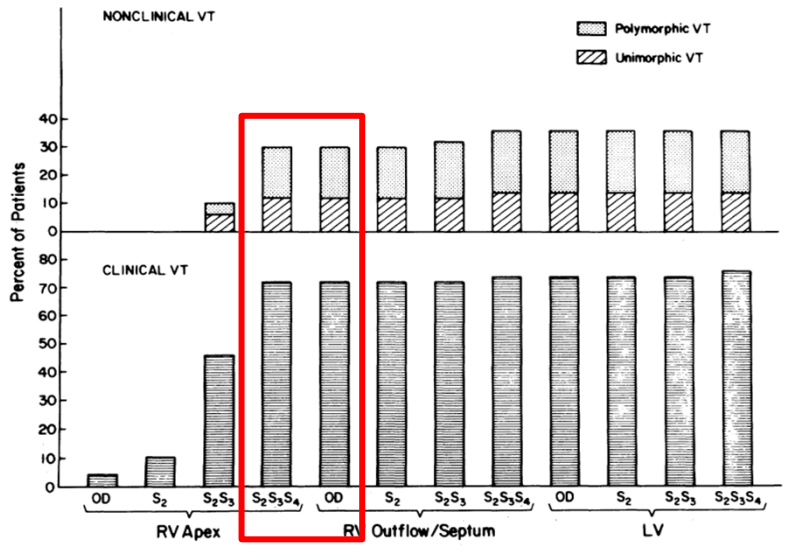


FIGURE 1. The cumulative yield of induced clinical and nonclinical ventricular tachycardia with protocol A in 50 patients with documented unimorphic ventricular tachycardia. RV = right ventricular; LV = left ventricular; OD = overdrive pacing; VT = ventricular tachycardia.

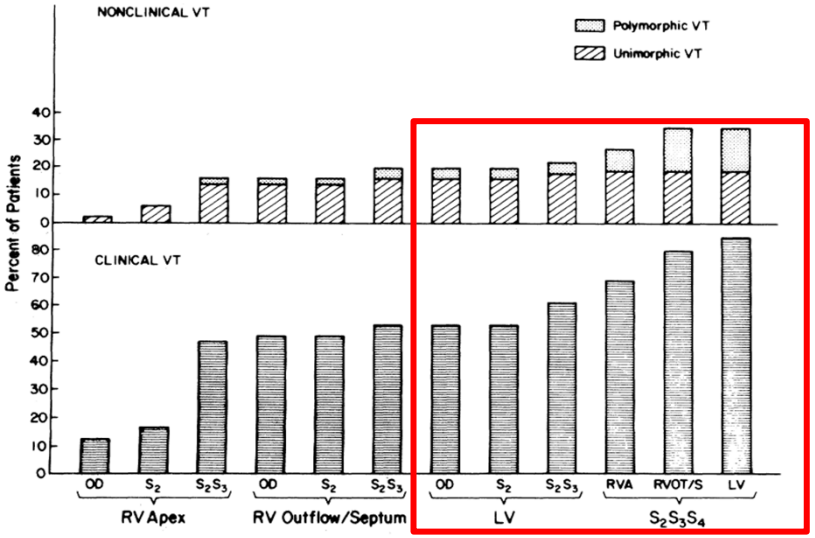


FIGURE 2. The cumulative yield of induced clinical and nonclinical ventricular tachycardia with protocol B in 51 patients with documented unimorphic ventricular tachycardia. OT = outflow tract; S = septum; other abbreviations are as in figure 1.

Circulation 70, No. 1, 52–57, 1984.

- RV stimulation first with triple extrastimuli: additional yield of clinical VT induced by LV stimulation is only 2%. Therefore, the use of triple extrastimuli in the RV will often preclude the need for LV stimulation.

- When a patient's spontaneous episodes of VT are well documented, one may wish to use protocol A (triple extrastimuli first), since nonclinical arrhythmias that may be induced will be readily identifiable as such.

- Suspected but undocumented VT (e.g., out-of-hospital cardiac arrest or unexplained syncope), it may be unclear whether induced VT is a clinically significant arrhythmia, especially if the tachycardia is polymorphic and induced by triple extrastimuli. For these patients we recommend use of protocol B (LV pacing first).

- Aggressive stimulation protocols involving three and four extrastimuli may produce a high incidence of nonclinical arrhythmias.

Circulation 70, No. 1, 52–57, 1984. Am Heart J. 1985 Sep;110(3):646-51.

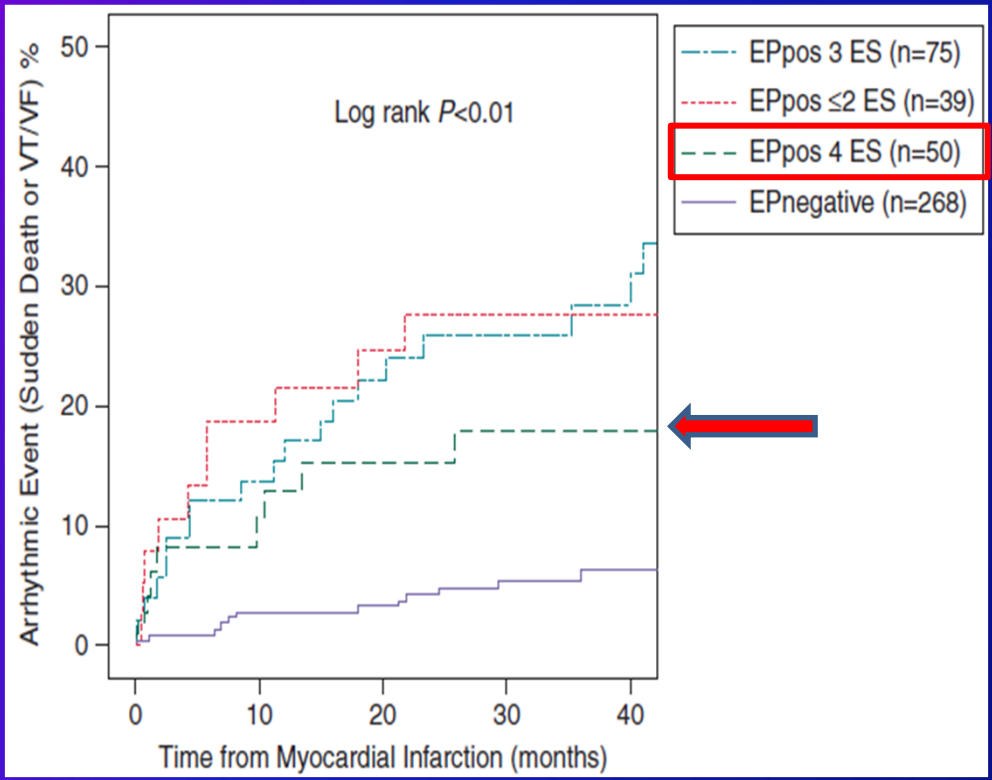
BCL 400ms with extrastimulus interval only once

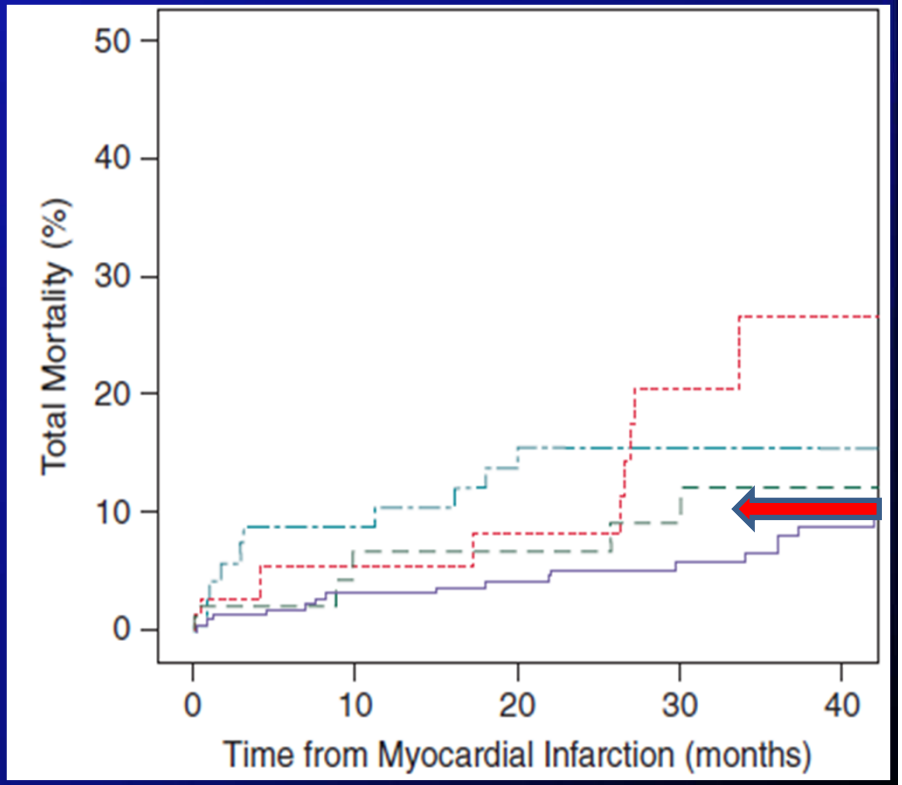
- Protocol A: BCL 400 ms with each extrastimulus coupling interval (CI) delivered only once.
- Protocol B: BCL 400 ms, each extrastimulus CI repeated three times before decrementing.
- Protocol C: BCL 300 ms without repetition of extrastimuli.
- 63%, 67%, and 63% of the study patients had VT inducible with protocols A, B, and C, respectively (P = NS). No significant differences in the mean CL of induced VT, the number of extrastimuli, and the CI of the last extrastimulus among the three protocols.
- **Rec protocol) BCL 400 ms with each extrastimulus interval only once (third or fourth extrastimulus)**

(J Cardiovasc Electrophysiol, Vol. 9, pp. 574-581, June 1998)

Fourth extrastimulus vs. less or equal to three extrastimulus

- After 3 years primary endpoint occurred in **28±8, 28±6, and 18±6%** in patients with VT induced with less than or **equal to two, three, and four ES,** respectively (P =0.31) and in 5±2% of EP-negative patients (P < 0.01).
- post-MI LV dysfunction, **VT can be induced in a significant proportion of patients with the fourth ES.** Comparable risk of arrhythmia to patients with inducible VT with less than or equal to three ES.





Europace (2012) **14**, 1771–1777

2. Forms of VT

- **VT associated with structural heart disease**
  - Infarct-related
  - Dilated cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Arrhythmogenic RV cardiomyopathy
  - Bundle branch reentry
- **Idiopathic VT**
  - RVOT
  - Idiopathic LV fascicular VT
  - Miscellaneous (LVOT, RV free wall)

3. EP study for structural heart disease

- Mechanism: reentrant
  - Scar: central obstacle around which the circuit revolves

- Generally be induced and often terminated by programmed ventricular stimulation

- Acute MI: early sustained monomorphic VT is relatively unusual and may represent an automatic or triggered rhythm rather than reentry related to arrhythmic substrate.

J Cardiovasc Electrophysiol, Vol. 15, pp. 908-910, August 2004.

4. EP study for idiopathic VT

1) Idiopathic RVOT VT

- Presumed mechanism: enhanced automaticity, triggered activity
  - Extrastimulus testing is limited use for VT induction.
- Facilitation of automaticity
  - isoproterenol, epinephrine, atropine and exercise.
- Triggered activity
  - multiple extrastimuli, burst pacing or short-long-short stimulus sequences, accompanied by the drugs and possibly aminophylline or calcium.
- Neuroleptic sedation is preferred over general anesthesia. **A degree of luck** are often necessary.

J Interv Card Electrophysiol (2015) 44:17–22

2) Idiopathic LV fascicular VT

- Mechanism: reentry involving a variable area of the LV inferior septum extending from base toward the apex, with the adjacent Purkinje network participating in the reentrant circuit

- Noninducibility of the clinical tachycardia is a major limitation. Difficulty in induction of VT in approximately 25–40% of the patients.

- Noninducibility may be due to deep sedation, suboptimal use of pharmacological agents, time constraints in the lab, or a combination of these factors.

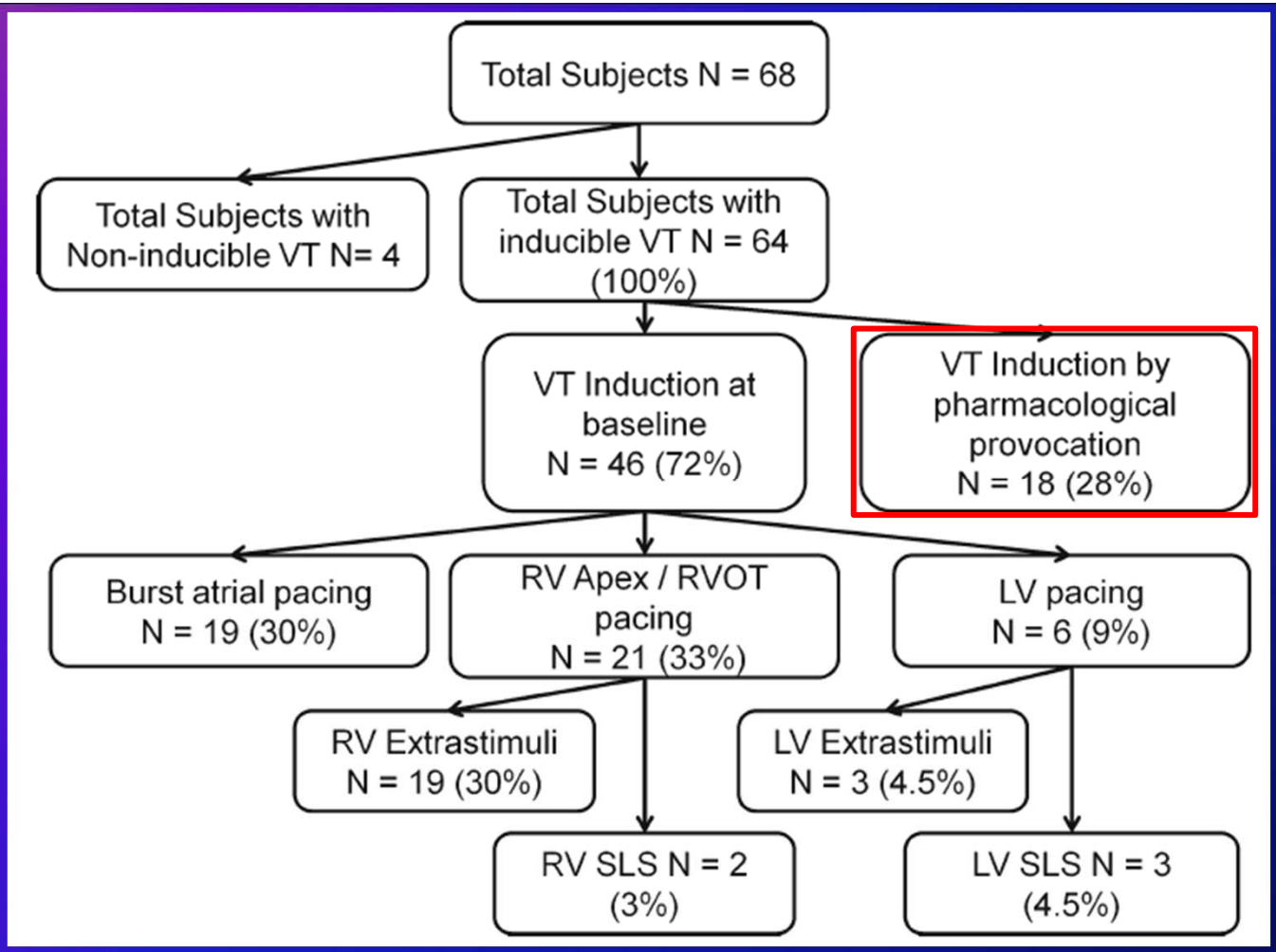
- **SLS sequence:** probable EP mechanism is the induction of bundle branch reentry by prolonging the refractory period of one of the branches of the circuit after the pause.

J Interv Card Electrophysiol (2015) 44:17–22

Induction protocol (Idioapthic fascucular VT)

- PVS (up to three extrastimuli at two BCLs of 500 and 400 ms)
- Baseline) S2:S3:S4 (400:350:300 and 350:300:250 ms) from RVA and then from RVOT
- **Non-inducible patients: SLS sequence, S1:S2:S3 (350:550:350 ms)** with decrements of 10 ms in S3, up to ventricular ERP or 200 ms was attempted.
- No induction: programmed stimulation from the LV using the same stimulation protocols.
- **No induction: pharmacological provocation.**
  - WCL ≥ 240 ms: isoprenaline or atropine
  - baseline WCL < 240 ms: IV phenylephrine.

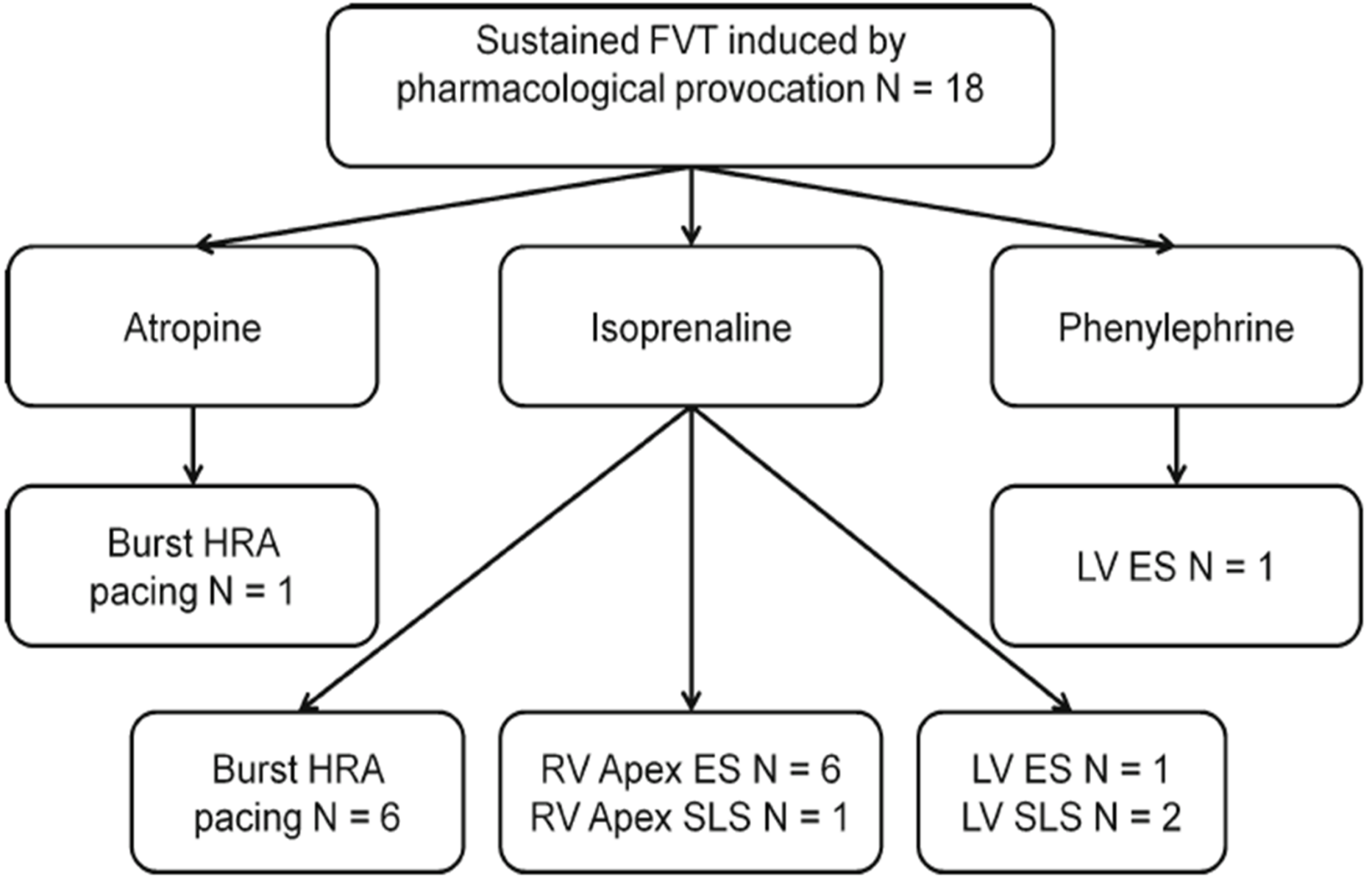
J Interv Card Electrophysiol (2015) 44:17–22



Results This systematic induction protocol was studied in 68 patients with clinically documented FVT and sustained FVT was inducible in 64 patients (94 %). Of these 64 patients, pharmacological provocation was required in 18 patients (28 %) while in the remaining, sustained VT was induced at baseline. This high induction rate allowed ablation during

J Interv Card Electrophysiol (2015) 44:17–22

Pharmacological provocation of fascicular VT



J Interv Card Electrophysiol (2015) 44:17–22

Infrequent intraprocedural PVC

- Infrequent intraprocedural PVCs: activation mapping difficulty, impeding the ablation procedure and resulting in reduced short- and long-term ablation success rates.
- Successful induction of PVCs with isoproterenol has been reported in, 50% of cases.
- Circadian distribution of PVCs is highly variable between patients, suggesting a more complex autonomic neural control.

(Heart Rhythm 2018;15:99–106)

5. Catecholamine

- **Target mechanism: triggered activity or abnormal automaticity**

- Shorten the ventricular refractory period, increase conduction velocity: allow more “aggressive” stimulation than can be delivered in their absence.

  - **Isoproterenol**
  - **Epinephrine**
  - **Dopamine**
  - **Dobutamine:** high dose (>10 *μ*g/kg/min)

J Cardiovasc Electrophysiol, Vol. 15, pp. 908-910, August 2004.

Adrenergic Nervous System Influences on the Induction of Ventricular Tachycardia

utive tests, exercise testing, isoproterenol infusion, and mental stress.

Methods: Nineteen subjects who experienced exercise test-induced ventricular tachycardia were subjected to an isoproterenol infusion and mental stress. All but one patient had cardiac disease, with 70% due to Chagas' disease. Seventeen of the 19 study subjects had normal ventricular function.

Results: Exercise test-induced ventricular tachycardia was nonsustained in 17 patients and sustained in 2 cases. Isoproterenol infusion induced nonsustained ventricular tachycardia in 9 of 19 patients. Mental stress, on its own, was able to induce nonsustained ventricular tachycardia in 2 of 19 patients.

Conclusions: Among patients preselected for exercise-induced ventricular tachycardia, almost half could be induced into ventricular tachycardia by isoproterenol infusion. Mental stress was a less powerful inducer of ventricular arrhythmias in this study group. **A.N.E. 2002;7(4):281–288**

- **Mental stress:** *arithmetic stress* was induced by subtracting a 2 digit number from one comprising 3 digits. If this proved to be too difficult, then the patient had to subtract 1 digit number from one containing 2 digits. The physician asked the patient to concentrate on the calculations and to *blame himself/ herself for lack of effort if the answers were wrong*. The test lasted for 2 minutes.

Isoproterenol

- **Beta-1 and Beta-2 agonist.**
- **Increases cAMP:** increased intracellular cAMP can decrease the resistance of cell-to-cell coupling, increasing the tissue conduction velocity. Increases the rate of rise of the zero phase of the cardiac action potential by increasing Na channel current.

J Electrocardiol. 1998 Apr;31(2):133-6.

- cAMP: triggered a transient inward current of Ca and resulted in **delayed after depolarization (DAD).**
- Sympathetic nervous system activity may have triggered DAD mediated by cAMP to **induce PVCs.**
- **Isoproterenol washout:** corresponds to a more complex situation mimicking exercise recovery, during sympathetic drive is decreasing, parasympathetic drive is progressively increasing in healthy subjects.

Heart, Lung and Circulation (2020) 29, 1152–1163

Phenylephrine

- **Alpha-adrenergic agonist:** induces vagal baroreflex activation, mediated through an acute rise in BP following vasoconstriction

- when PVCs were not sustainably present at baseline or during isoproterenol infusion/washout

- Phenylephrine (repeated boluses) was used in order to obtain a 25% increase in systolic BP (~ 30 mm Hg) triggering a vagal response decreasing HR (~ 10%).

J Cardiovasc Electrophysiol. 2019;30:836–843.

6. Circadian different patterns of arrhythmias

- **Morning hours**
  - long QT syndrome type 1 and 2, post–MI, and among deaths due to cardiac arrest.
- **Afternoon and evening hours**
  - hypertrophic cardiomyopathy
- **Nocturnal ventricular arrhythmias**
  - LQTS3, Brugada syndrome

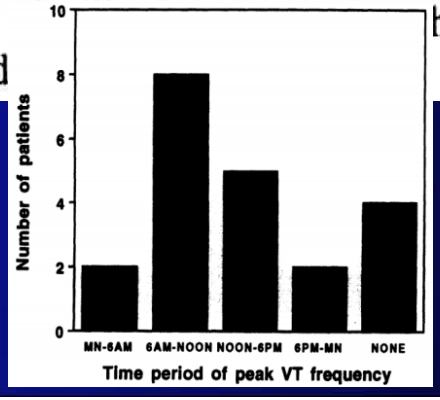
J Am Coll Cardiol EP 2017;3:1308-17

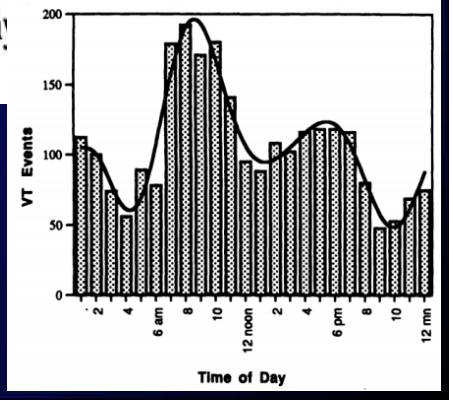
Circadian Variation of Sustained Ventricular Tachycardia in Patients With Coronary Artery Disease and Implantable Cardioverter-Defibrillators

Background While previous studies using epidemiological data and ambulatory ECG monitoring have shown peak occurrence of sudden death and nonsustained ventricular tachycardia in the morning, none have examined circadian variation of potentially life-threatening ventricular tachycardia (VT), nor has any study observed circadian behavior of any arrhythmias in individuals followed longitudinally. We used the event memory of multiprogrammable implantable cardioverter-defibrillators to evaluate the circadian pattern of sustained VT over time.

Methods and Results Data were reviewed from 32 consecutive patients with coronary artery disease and sustained VT who had received the Ventak PRX (CPI, Inc) cardioverter-defibrillator between May 1991 and August 1993 and had experienced at least one episode of VT terminated by their device. Mean follow-up was 14±7 months. Among the 2558 episodes recorded by the device logs, VT occurrence peaked between 6 AM and noon (P=.007 by ANOVA among four 6-hour time periods). Harmonic regression revealed a morning peak at 9 AM (P<.01). This morning peak occurred in patients with both frequent and infrequent events. Among 21 patients who experienced more than four VT events, 8 (38%) had an AM peak of VT occurrence (>35% of VT between 6 AM and noon). Neither age, ejection fraction, event frequency, presenting arrhythmia, nor drug therapy distinguished patients who displayed the AM VT peak.

Conclusions In patients with coronary artery disease, sustained VT displays circadian variation with peak frequency in the morning, similar to that for sudden death. Individual patients who display specific patterns of circadian variation over time can be identified using defibrillator logs. Investigation of circadian variation of other phenomena to elucidate mechanisms of VT should focus on these patients. (***Circulation*. 1994;90:241-247.**)





Circadian, Daily, and Seasonal Distributions of Ventricular Tachyarrhythmias in Patients With Implantable Cardioverter-Defibrillators

from 154 consecutive patients (mean age 67 ± 14 years; 78% men, 71% with ischemic heart disease [IHD], mean left ventricular ejection fraction 34 ± 15%) were analyzed. During a mean follow-up of 35 ± 19 months, a total of 1,055 episodes of spontaneously terminated ventricular tachycardia (VT) and 612 episodes of VT or ventricular fibrillation with appropriate device

the greatest incidence in the winter months and the lowest incidence in summer, spring, and fall. A linear regression between the number of episodes and the average daily temperature showed a greater likelihood of the 2 events occurring on cooler days, irrespective of the cause of cardiac disease. A weekly distribution was also observed, with the greatest proportion of episodes occurring on Fridays and the lowest on Saturdays and Sundays. A bimodal circadian distribution was present, with the greatest peak occurring from 8 A.M. to 1 P.M. and a smaller peak occurring from 5 P.M. to 10 P.M. In conclusion, the occurrence of ventricular tachyarrhythmias appears to follow circadian, daily, and seasonal distributions that are similar in patients with IHD and non-IHD. The incidence inversely correlates with average daily temperatures. (Am J Cardiol 2007;100:

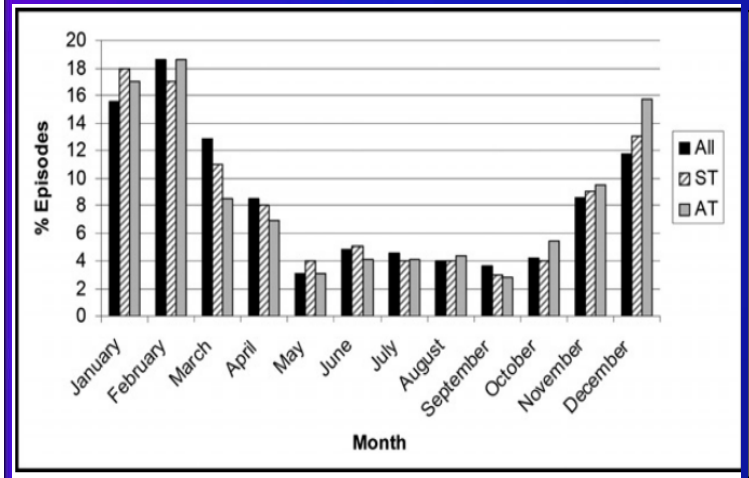


Figure 1. Annual distribution of ventricular tachyarrhythmias.

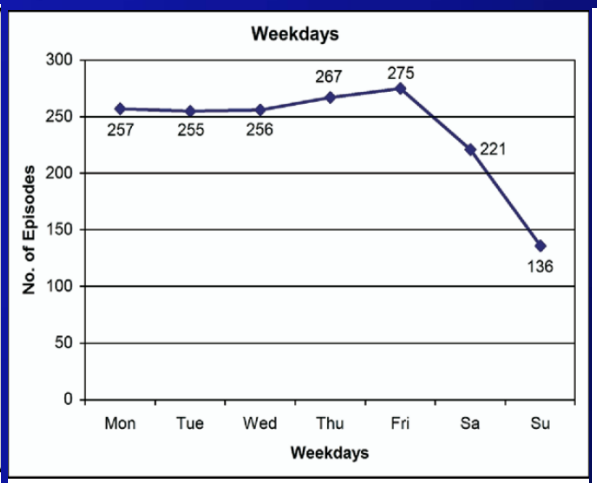


Figure 4. Weekly distribution of all ventricular tachyarrhythmias.

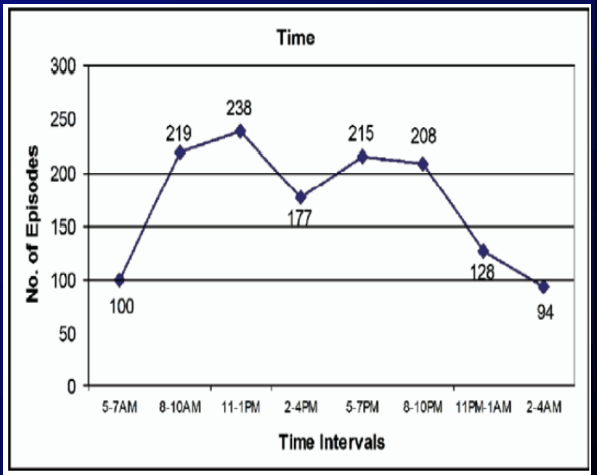


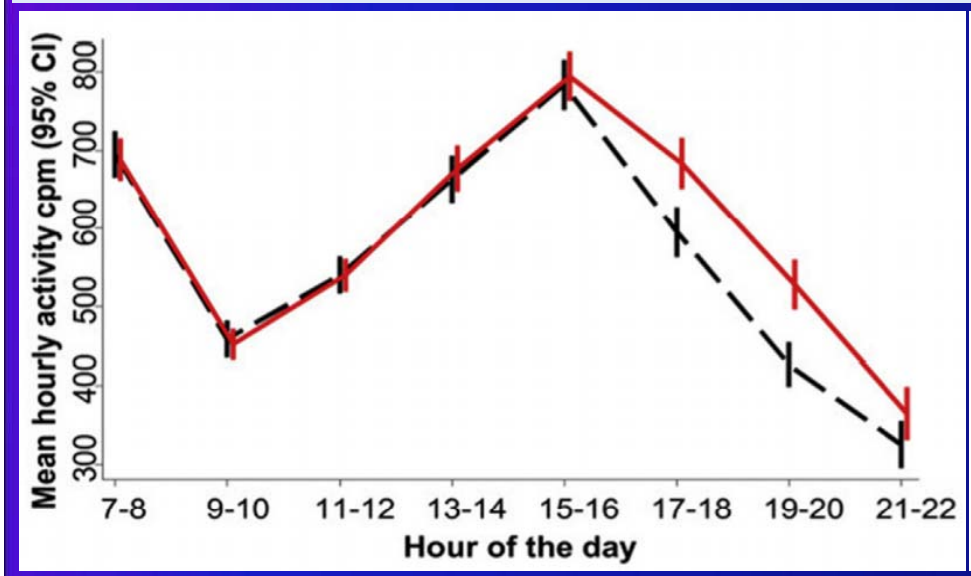
Figure 5. Circadian distribution of all ventricular tachyarrhythmias.

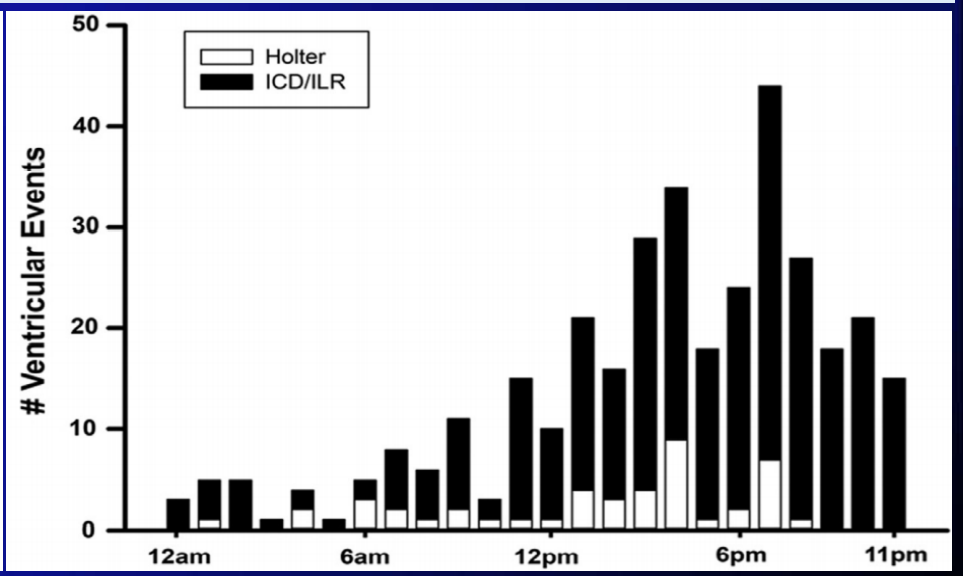
Am J Cardiol 2007;100:1134–1138

Circadian Variation of Ventricular Arrhythmias in Catecholaminergic Polymorphic Ventricular Tachycardia

RESULTS Eighty patients (53% male), 61% with an ICD, experienced 423 VT events during a median follow-up time of 6 years (interquartile range: 2 to 10 years). When compared to morning hours, VT was more likely to occur in the afternoon (odds ratio [OR]: 2.54; 95% confidence interval [CI]: 1.69 to 3.83) or evening hours (OR: 2.91; 95% CI: 1.82 to 4.67). The predominance of afternoon/evening events persisted regardless of age, gender, or day of the week. Among 50 patients who underwent exercise stress tests, VT was significantly more likely to occur in the afternoon (OR: 3.00; 95% CI: 1.39 to 6.48).

CONCLUSIONS In pediatric CPVT patients, ventricular arrhythmias are more likely to occur in the afternoon and evening hours. Because children's activity levels peak in both the morning and afternoon, the lack of arrhythmias in the morning hours raises questions whether factors other than adrenergic stimulation influence arrhythmia induction in pediatric patients with CPVT. (J Am Coll Cardiol EP 2017;3:1308–17)





J Am Coll Cardiol EP 2017;3:1308–17

VT/PVCs influenced by autonomic nerve imbalance

- PVC and VT occurrence: associated with different circadian rhythms, which may be related to the autonomic nerve imbalance.
- Sympathetic hyperactivity: favors the onset of life-threatening VT
- Vagal activation: protective effect. VT/PVCs is usually attenuated by beta blockers.

Heart, Lung and Circulation (2020) 29, 1152–1163

Circadian variability patterns of PVCs

- PVC burden (≤11.7%) and at least 2 hours with <120 PVCs on a 24-hour Holter recording best **predicted unsuccessful ablation**
- Fast-HR-dependent PVC: responded to isoproterenol.
- Slow-HR-dependent PVC: Isoproterenol washout or phenylephrine infusion
- Independent-HR-PVC: no drug could increase PVC frequency

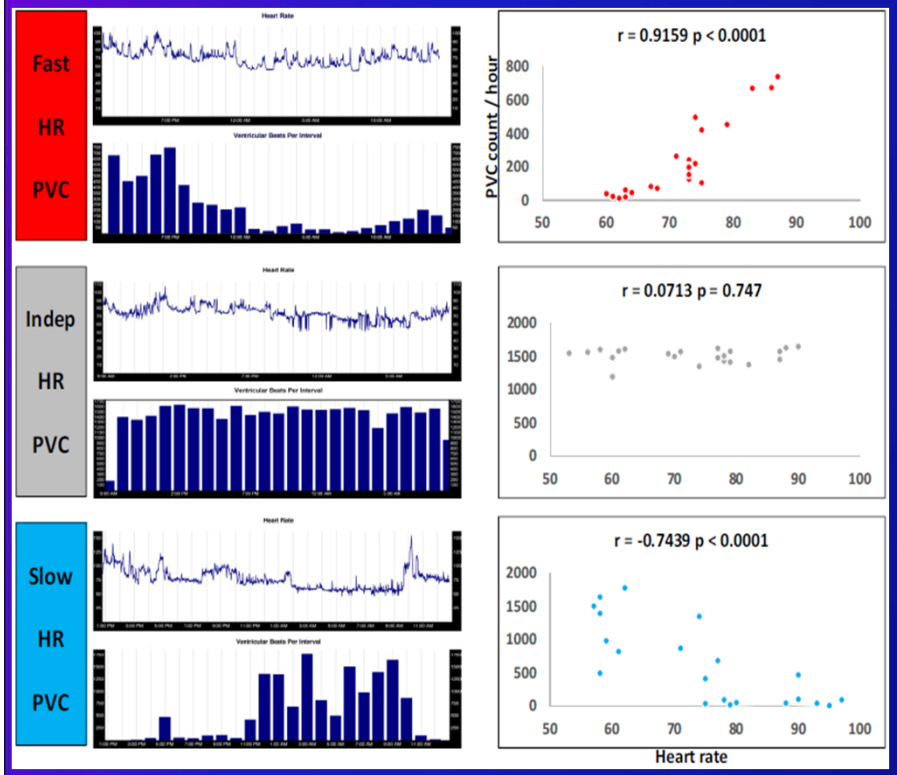


Table 3 Response to different drugs during EPS in patients with infrequent intraprocedural PVC at baseline

Patients needing drug infusion	Isoproterenol infusion	Isoproterenol washout	Phenylephrine infusion	Epinephrine infusion
All n (% success)	15/31 (48.4)	3/16 (18.7)	1/9 (11.1)	0/6 (0)
Fast-HR-PVC	15/16 (93.7)	0/1 (0)	0/1 (0)	Ø
Independent-HR-PVC	0/12 (0)	0/12 (0)	0/7	0/6 (0)
Slow-HR-PVC	0/3 (0)	3/3 (100)	1/1 (100%)	Ø

(Heart Rhythm 2018;15:99–106)

Premature ventricular contraction diurnal profiles predict distinct clinical characteristics and beta-blocker responses

Results: Of the 416 patients included, 50.2% had F-HR-PVC, 35.6% I-HR-PVC, and 14.2% S-HR-PVC with distinct clinical profiles. Beta-blocker therapy was successful in 34.0% patients overall: patients with F-HR-PVC had a decrease in PVC burden (18.8 ± 10.4% to 9.3 ± 6.6%, $P < 0.0001$; 62% success), I-HR-PVC had no change (18.4 ± 17.9% to 20.6 ± 17.9%, $P = 0.175$; 0% success), whereas S-HR-PVC had an increase in burden (14.6 ± 15.3% to 20.8 ± 13.8%, $P = 0.016$; 0% success). The correlation coefficient was the only

Conclusions: A simple analysis of Holter PVC diurnal variability may provide incremental value to guide clinical PVC management. Only patients displaying a F-HR-PVC profile benefited from beta-blockers. An alternative strategy should be considered for others, as beta-blockers may have no effect or can even be harmful.

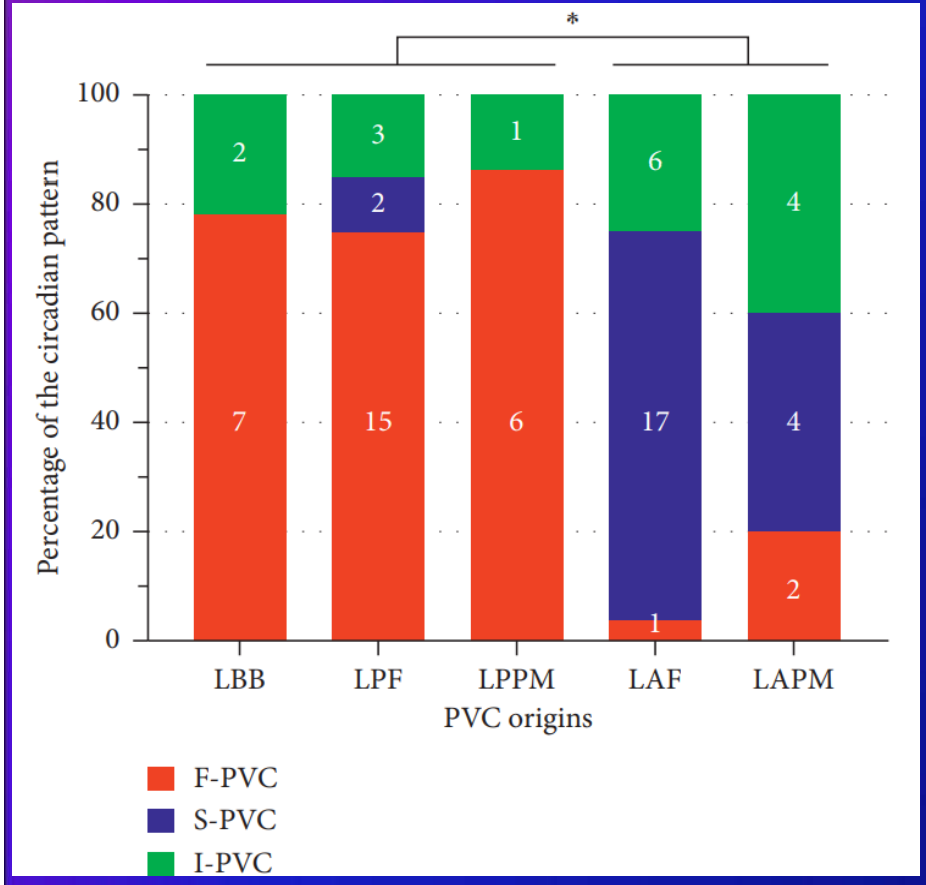
J Cardiovasc Electrophysiol. 2019;30:836–843.

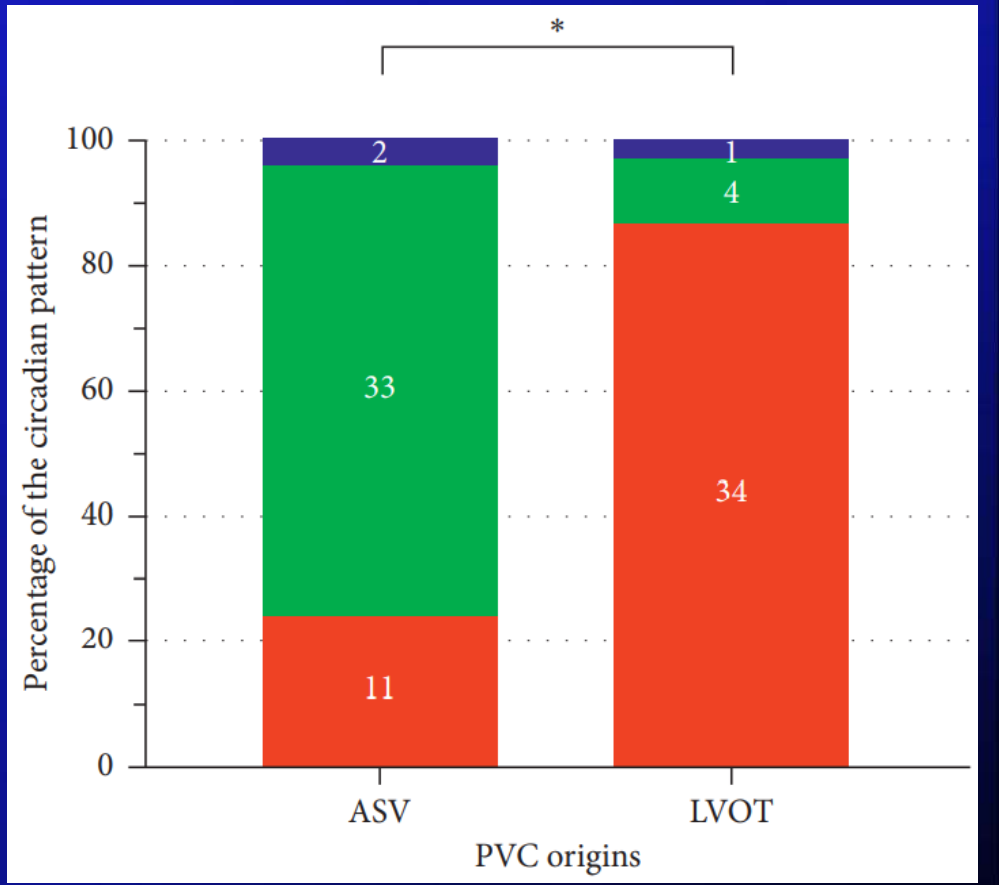
- **Autonomic function plays a key role in arrhythmogenesis**
  - I-HR-PVC profile: independent from autonomic variation
  - F-HR-PVC type: evoked by adrenergic triggers
  - S-HR-PVC: more likely by vagal triggers
- Avoiding the use of beta-blockers in the S-HR-PVC pattern patients (typically young, healthy women) because of its potential paradoxical harmful effect on PVC burden.
- Flecainide, a weakly vagolytic class IC, may represent a suitable option for these patients when indicated or preferred over an ablation strategy, but further data are needed.

J Cardiovasc Electrophysiol. 2019;30:836–843.

Utility of Circadian Variability Patterns in Differentiating Origins of Premature Ventricular Complexes

- fast-HR-dependent (F-PVC), slow-HR-dependent (S-PVC), and HR-independent (I-PVC)





PVCs originating from right ventricles, such as RVOT, did not show distinct circadian patterns.

J Interv Cardiol. 2020 Oct 30;2020:7417912.

Take home message

1. **Programmed ventricular stimulation (PVS)**
   - Basic cycle length (BCL): (S1) (CL 600 ms and 400 ms)
     - Ventricular burst pacing, Incremental ventricular pacing
   - Number of extrastimuli (main mechanism: reentrant)
     - Single, Double, Triple (S2/S3/S4), SLS sequences
     - Site of stimulation: RV apex, RVOT, and LV

2. **EP study for SHD, idiopathic VT**

3. **Catecholamine**
   - **Isoproterenol, Epinephrine, Dopamine, Dobutamine**
   - **Phenylephrine**

4. **Circadian different patterns of arrhythmias**

Thank you for your attention ‴ ^^