Mechanisms of PVC Induced Cardiomyopathy

Seil Oh, **MD, PhD, FHRS, FESC**

Professor of Medicine

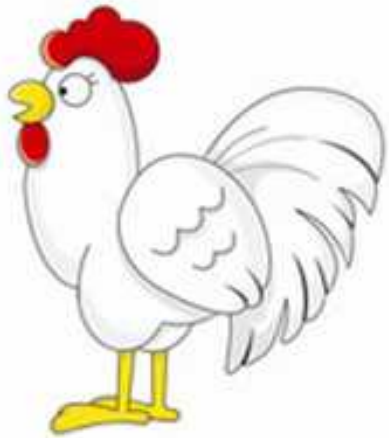
Seoul National University

Today's Issue

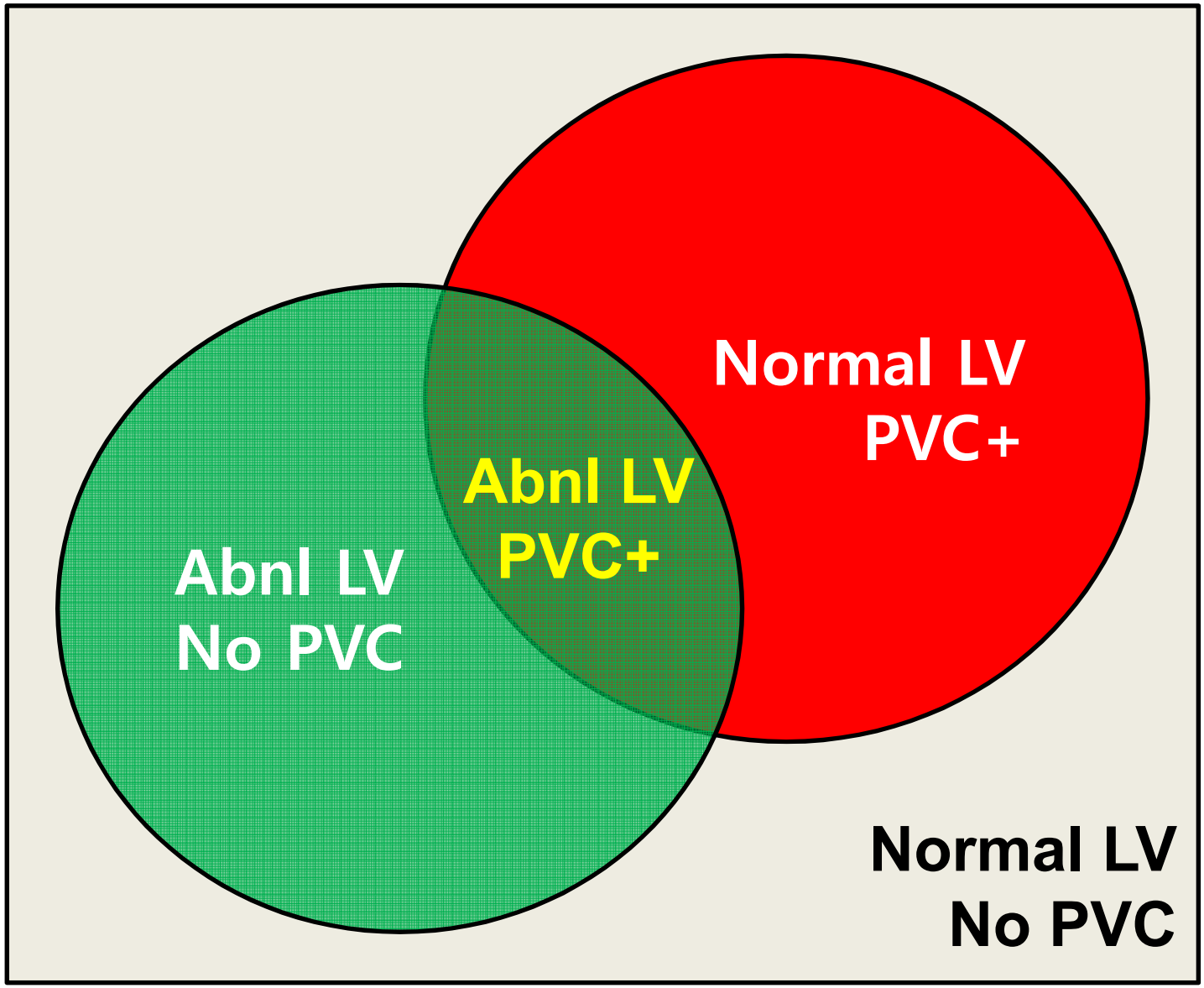
Frequent ventricular ectopy in Pts without structural heart disease may induce LV dilatation / dysfunction.

Dilemma: the chicken or the egg

LV dysfunction:



High PVC burden:


Normal LV
PVC+
AbnI LV
PVC+
AbnI LV
No PVC
Normal LV
No PVC

PVC-induced cardiomyopathy (PIC)

- In general, Pts with PVCs w/o structural heart disease
  - Benign clinical course
  - Treatment: reserved for symptomatic improvement

- In some Pts with frequent PVCs
  - Decrease in ventricular function or chamber dilatation

Other arrhythmia-induced cardiomyopathies

- Most of which are tachycardia-mediated (atrial fibrillation being the most common).
- Rhythm irregularity has also been proposed as a mechanism for cardiomyopathy in AF.
- Frequent PACs may also result in cardiomyopathy, but the detrimental effect of PACs appears to be less than that of PVCs (based on animal studies).

Can frequent PVCs aggravate LV EF?

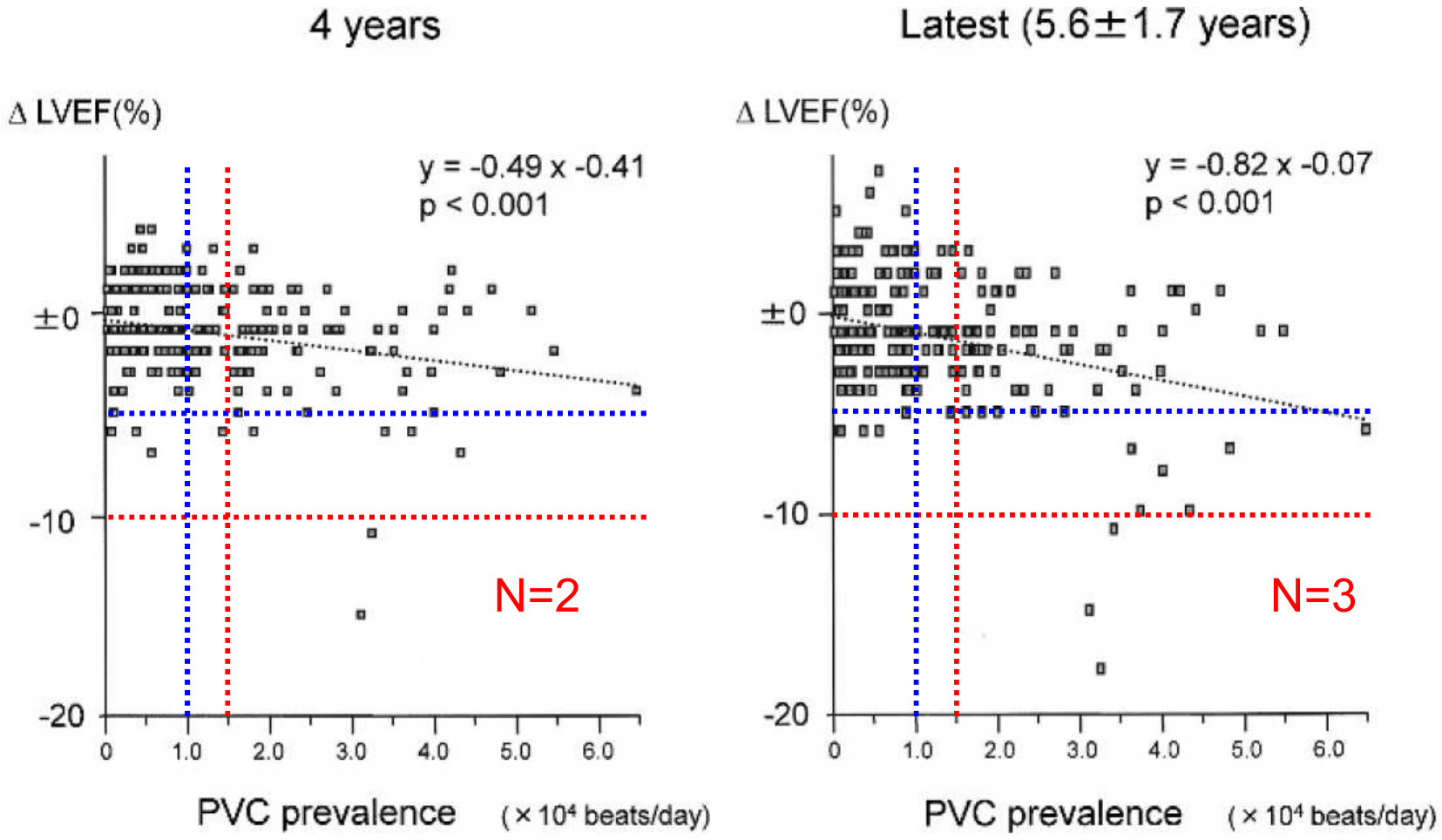
Prognostic significance of frequent premature ventricular contractions originating from the ventricular outflow tract in patients with normal left ventricular function

239 patients, > 4-year Observation

any detectable heart disease. Most of the patients were asymptomatic and assigned to further examination due to the recording of frequent PVCs in the 12-lead ECG in a routine health check. The

Niwano S. Heart 2009;95:1230–1237

Prognostic significance of frequent premature ventricular contractions originating from the ventricular outflow tract in patients with normal left ventricular function



Niwano S. Heart 2009;95:1230–1237

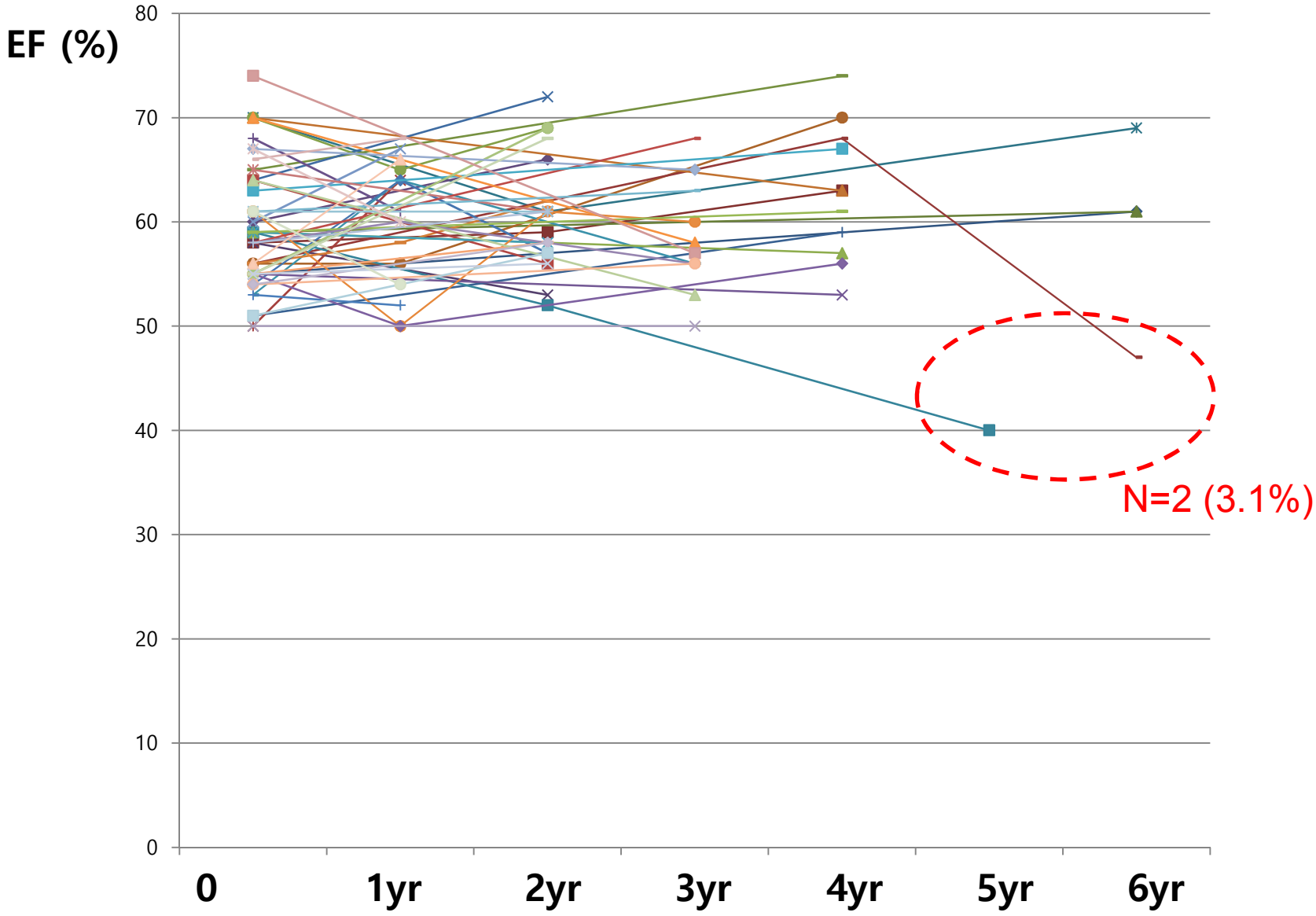
SNUH Experience

- PVC (>10%) cohort with normal heart (LVEF > 50%)
- F/U duration: 33±16 months (7-78 months)

- Incidence of LV function depression (ΔEF < -5%)
  - 13/64 (20%)

Lee SR / Oh S. Unpublished data.

LV EF Changes of All Patients



Lee SR / Oh S. Unpublished data.

PIC: Diagnosis

- Presumptively based on
  - Presence of frequent PVCs
  - Existing cardiomyopathy
  - No alternative etiology for the cardiomyopathy

Diagnosis

- Pts with relatively low PVC burdens
  - Causal relationship between the PVCs and the cardiomyopathy can be challenging
  - Only verified when elimination of the PVCs results in resolution of the cardiomyopathy

Predisposing Factors of PIC

- PVC burden
  - Persistent PVC duration
  - Longer duration of PVC exposure
  - Burden of interpolated PVC
  - Multiform PVC
- PVCs with longer QRS duration
- Origin of PVC
  - Epicardial origin
  - RV origin (greater LV dyssynchrony)
- Presence of NSVT
- Lack of diurnal variation of PVC frequency
- Male sex

Latchamsetty R & Bogun F. J Am Coll Cardiol EP 2019;5:537–50.
Lu F et al. Am J Cardiol 2012;110:852-6.
del Carpio Munoz F et al. J Cardiovasc Electrophysiol 2011;22:791-8.
Yokokawa M et al. Heart Rhythm 2012;9:1460-4.
Olgun H et al. Heart Rhythm 2011;8:1046-9.

Relationship between burden of premature ventricular complexes and left ventricular function

Timir S. Baman, MD,* Dave C. Lange, MD,* Karl J. Ilg, MD,* Sanjaya K. Gupta, MD,* Tzu-Yu Liu, MS,† Craig Alguire, MD,* William Armstrong, MD, FACC,* Eric Good, DO, FACC,* Aman Chugh, MD, FACC,* Krit Jongnarangsin, MD,* Frank Pelosi, Jr., MD,* Thomas Crawford, MD,* Matthew Ebinger, MD, DO,* Hakan Oral, MD, FACC,* Fred Morady, MD, FACC,* Frank Bogun, MD, FACC*

*From the *Division of Cardiovascular Medicine and the*
†Department of Electrical Engineering and Computer Science, University of Michigan, Ann Arbor, Michigan.

BACKGROUND Frequent idiopathic premature ventricular complexes (PVCs) can result in a reversible form of left ventricular dysfunction. The factors resulting in impaired left ventricular function are unclear. Whether a critical burden of PVCs can result in cardiomyopathy has not been determined.

OBJECTIVE The objective of this study was to determine a cutoff PVC burden that can result in PVC-induced cardiomyopathy.

METHODS In a consecutive group of 174 patients referred for ablation of frequent idiopathic PVCs, the PVC burden was determined by 24-hour Holter monitoring, and transthoracic echocar-

RESULTS A reduced left ventricular ejection fraction (mean 0.37 ± 0.10) was present in 57 of 174 patients (33%). Patients with a decreased ejection fraction had a mean PVC burden of 33% ± 13% as compared with those with normal left ventricular function 13% ± 12% (P <.0001). A PVC burden of >24% best separated the patient population with impaired as compared with preserved left ventricular function (sensitivity 79%, specificity 78%, area under curve 0.89) The lowest PVC burden resulting in a reversible cardiomyopathy was 10%. In multivariate analysis, PVC burden (hazard ratio 1.12, 95% confidence interval 1.08 to 1.16; P <.01) was independently associated with PVC-induced cardiomyopathy.

CONCLUSION A PVC burden of >24% was independently associated with PVC-induced cardiomyopathy.

Pts with LVEF < 50% had high PVC burden.
PVC burden > 24% was associated with PIC.

RVOT = right ventricular outflow tract

(Heart Rhythm 2010;7:865–869)

Y

PVC burden is very variable

HOLTER REPORT

Patient: YOU

SEOUL NATIONAL UNIVERSITY HOSP.

ID: 19463148
DoB/Age: 70 yr

Edit Date: 24-FEB-2018
Hook-up Date: 22-FEB-2018

Indications:
Medications:
Referred by:

98454 QRS complexes
24272 Ventricular ectopics which rep
53 Supraventricular ectopics whi
0 Paced QRS complexes which

VENTRICULAR ECTOPY
24260 Isolated
4063 Bigeminal Cycles
6 Couplets
0 Runs
0 Beats in Runs
Beats LONGEST at BPM at
Beats FASTEST at BPM at

S-T LEVELS Channel 1

HEART RATES
46 MIN at 03:02:08 23-FEB-201
71 AVG
108 MAX at 17:54:25 22-FEB-20

HOLTER REPORT

Patient: YOU

SEOUL NATIONAL UNIVERSITY HOSP.

ID: 19463148
DoB/Age: 71 yr
Sex: Male

Edit Date: 14-JUN-2019
Hook-up Date: 13-JUN-2019
Time: 10:57:00
Duration: 23:19:00

Indications:
Medications:
Referred by:

SUMMARY

89604 QRS complexes
19 Ventricular ectopics which represent <1 % of total QRS complexes
68 Supraventricular ectopics which represent <1 % of total QRS complexes
0 Paced QRS complexes which represent <1 % of total QRS complexes

VENTRICULAR ECTOPY
17 Isolated
0 Bigeminal Cycles
1 Couplets
0 Runs
0 Beats in Runs
Beats LONGEST at BPM at
Beats FASTEST at BPM at

SUPRAVENTRICULAR ECTOPY
61 Isolated
2 Couplets
1 Runs
3 Beats in Runs
3 Beats LONGEST at 91 BPM at 03:08:50 14-JUN-2019
3 Beats FASTEST at 91 BPM at 03:08:50 14-JUN-2019

S-T LEVELS Channel 1 S-T LEVELS Channel 2 S-T LEVELS Channel 3

HEART RATES
45 MIN at 03:33:34 14-JUN-2019
64 AVG
98 MAX at 13:46:41 13-JUN-2019

LONGEST RR 1.840 sec at 03:08:52 14-JUN-2019

INTERPRETATION

Impact of QRS duration of frequent premature ventricular complexes on the development of cardiomyopathy

Miki Yokokawa, MD, Hyungjin Myra Kim, ScD, Eric Good, DO, Thomas Crawford, MD, Aman Chugh, MD, Frank Pelosi Jr, MD, Krit Jongnarangsin, MD, Rakesh Latchamsetty, MD, William Armstrong, MD, Craig Alguire, MD, Hakan Oral, MD, Fred Morady, MD, Frank Bogun, MD

From the Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan.

BACKGROUND Patients with frequent premature ventricular complexes (PVCs) are at risk of developing reversible PVC-induced cardiomyopathy (rPVC-CMP). Not all determinants of rPVC-CMP are known.

OBJECTIVE To assess the impact of the QRS duration of PVCs on the development of rPVC-CMP.

METHODS In a consecutive series of 294 patients with frequent idiopathic PVCs referred for PVC ablation, the width of the PVC-QRS complex was assessed. The QRS width was correlated with the presence of rPVC-CMP.

Broader PVC (esp. ≥ 150 ms) and Epicardial origin

right ventricular outflow tract or the fascicles had the narrowest QRS complexes. After adjusting for PVC burden, symptom duration, and PVC site of origin, PVC-QRS width and an epicardial PVC origin were independently associated with rPVC-CMP. Based on receiver operator characteristics analysis, a QRS duration of >150 ms best differentiated patients with and without rPVC-CMP (area under the curve 0.66; sensitivity 80%; specificity 52%). The PVC burden for developing rPVC-CMP is significantly lower in patients with a PVC-QRS width of ≥150 ms than in patients with a narrower PVC-QRS complex (22% ± 13% vs 28% ± 12%; $P < .0001$).

CONCLUSION Broader PVCs and an epicardial PVC origin are associated with the development of rPVC-CMP independent of the PVC burden.

(Heart Rhythm 2012;9:1460–1464)

Predictors of recovery of left ventricular dysfunction after ablation of frequent ventricular premature depolarizations

Marc W. Deyell, MD, MSc, Kyoung-Min Park, MD, Yuchi Han, MD, MSc, David S. Frankel, MD, Sanjay Dixit, MD, FHRS, Joshua M. Cooper, MD, Mathew D. Hutchinson, MD, FHRS, David Lin, MD, Fermin Garcia, MD, Rupa Bala, MD, Michael P. Riley, MD, PhD, Edward Gerstenfeld, MD, FHRS, David J. Callans, MD, FHRS, Francis E. Marchlinski, MD, FHRS

From the Electrophysiology Section, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

BACKGROUND Frequent ventricular premature depolarizations (VPDs) can cause reversible left ventricular (LV) dysfunction. However, not all patients normalize their LV function after VPD elimination.

OBJECTIVE To evaluate predictors of recovery of LV function following the elimination of frequent VPDs.

METHODS We identified patients with ≥10% VPDs/24 h and an LV ejection fraction of <50% who underwent successful ablation between 2007 and 2011. Subjects were classified as having reversible (≥10% increase to a final LV ejection fraction of ≥50%) or irreversible (≤10% increase or final LV ejection fraction <50%) LV dysfunc-

ible and 13 of 48 as irreversible and 11 of 44 were excluded. There was a gradient of VPD QRS duration between the control, reversible, and irreversible groups (mean VPD QRS 135, 158, and 173 ms, respectively; $P < .001$). This gradient persisted even for the same site of origin. In multivariate analysis, the only independent predictor of irreversible LV function was VPD QRS duration (odds ratio 5.07 [95% confidence interval 1.22–21.01] per 10-ms increase).

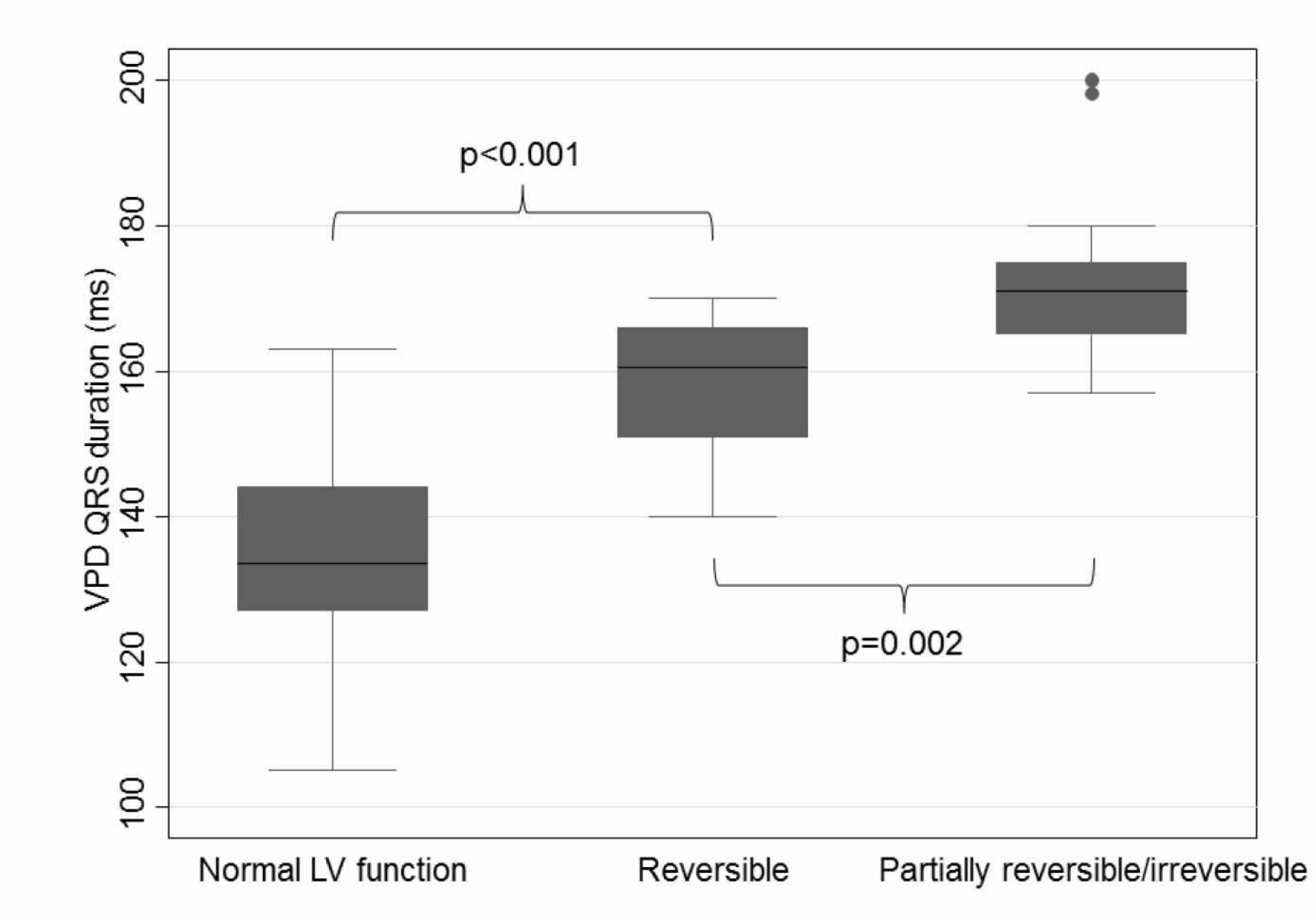
CONCLUSION In patients with LV dysfunction and frequent VPDs, we identified VPD QRS duration as the only independent predictor for the recovery of LV function after ablation. This suggests that VPD QRS duration may be a marker for the severity of underlying substrate abnormality.

KEYWORDS Cardiomyopathy; Catheter ablation; Electrocardio-

QRS duration: independent predictor for recovery of LV EF after RFCA

(Heart Rhythm 2012;9:1465–1472)

PVC QRS Duration & Reversibility of LV dysfunction



Deywll MW / Marchlinski FE. Heart Rhythm. 2012;9:1465-1472

Characteristics of Premature Ventricular Complexes as Correlates of Reduced Left Ventricular Systolic Function: Study of the Burden, Duration, Coupling Interval, Morphology, and Site of Origin of PVCs

FREDDY DEL CARPIO MUNOZ, M.D.,* FAISAL F. SYED, M.B.C.H.B.,†
AMIT NOHERIA, M.B.B.S., S.M.,‡ YONG-MEI CHA, M.D.,* PAUL A. FRIEDMAN, M.D.,*
STEPHEN C. HAMMILL, M.D.,* THOMAS M. MUNGER, M.D.,*
K.L. VENKATACHALAM, M.D.,¶ WIN-KUANG SHEN, M.D.,*
DOUGLAS L. PACKER, M.D., F.H.R.S.,* and SAMUEL J. ASIRVATHAM, M.D., F.H.R.S.*,§

From the *Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA; †Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA; ‡Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California, USA; ¶Division of Cardiovascular Diseases, Mayo Clinic, Jacksonville, Florida, USA; and §Division of Pediatric Cardiology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

PVCs and Left Ventricular Dysfunction. ***Background:*** **Frequent premature ventricular complexes (PVCs) can cause a decline in left ventricular ejection fraction (LVEF). We investigated whether the site of origin and other PVC characteristics are associated with LVEF.**

Methods: **We retrospectively studied 70 consecutive patients (mean age 42 ± 17 years, 40 [57%] female) with no other cause of cardiomyopathy undergoing ablation of PVCs. We analyzed the association of a reduced LVEF, defined by LVEF <50% on echocardiography, with features of PVCs obtained from electrocardiography, 24- or 48-hour Holter monitor and electrophysiology study.**

Results: **Patients with reduced LVEF (n = 17) as compared to normal LVEF (n = 53) had an increased**

Pts with LV EF < 50% had high PVC burden (29.3% vs. 16.7%), wider QRS, higher prevalence of multiform PVCs and RV PVCs.

burden of PVCs associated with reduced LVEF was lower for right as compared to left ventricular PVCs.

Conclusion: **In addition to the PVC burden, other characteristics like a longer PVC duration, presence of nonsustained VT, multiform PVCs and right ventricular PVCs might be associated with cardiomyopathy.**

(J Cardiovasc Electrophysiol, Vol. 22, pp. 791-798, July 2011)

High PVC burden is observed in

Pts with LV dysfunction

≠

High PVC burden is

the culprit of LV dysfunction

- Retrospective studies
- Cross-sectional observation data

➔ Causal relationship ?

Mechanisms of PIC

PIC Model

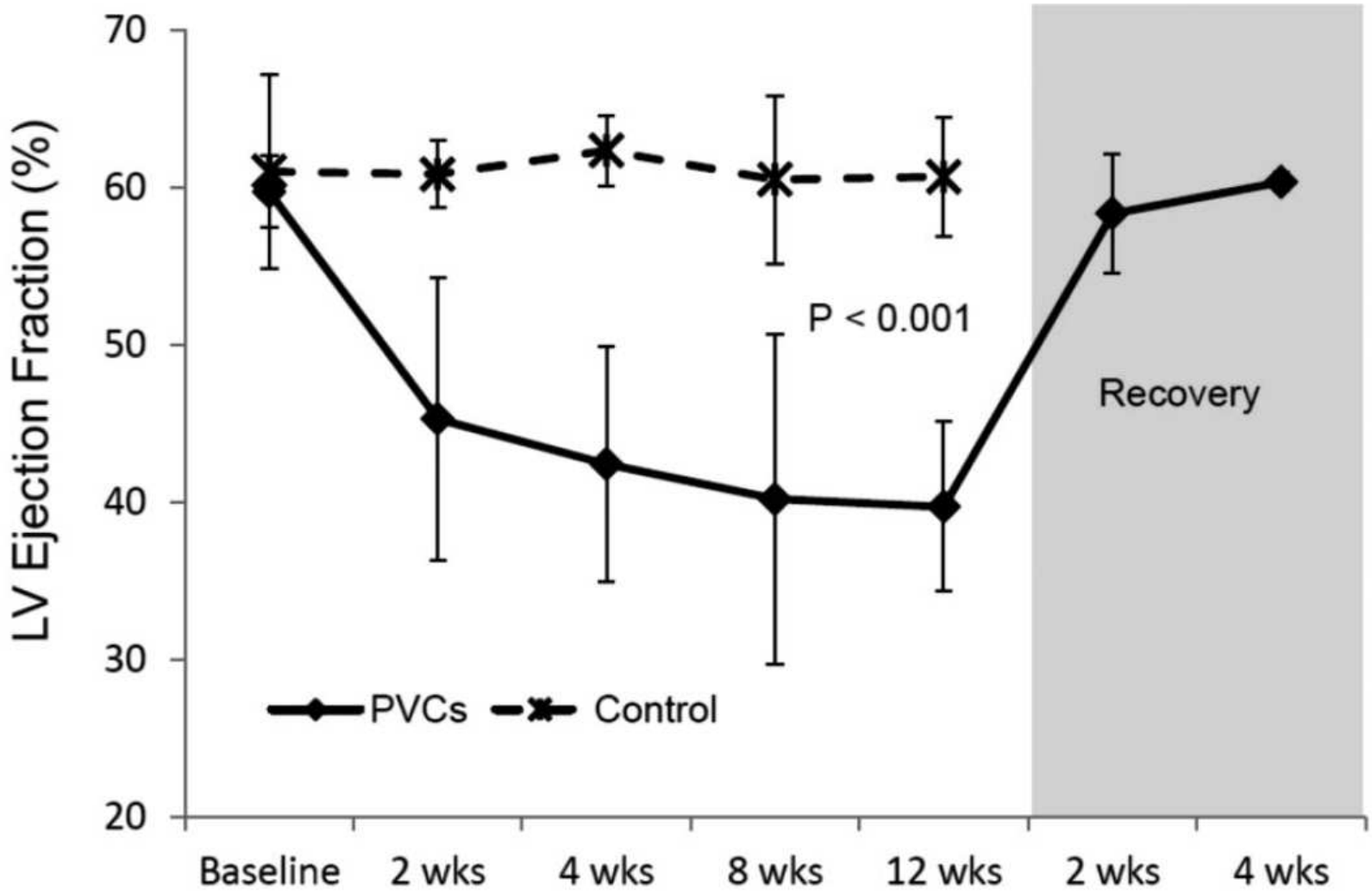
- Fourteen mongrel dogs

- Pacing system
  - Bipolar epicardial lead (Medtronic) at RV apex
  - Single chamber pacemaker (SJM) with a unique algorithm

- PVC
  - Fixed coupling interval 250 ms
  - Burden 50% (bigeminy)

Huizar JF et al. Circ Arrhythm Electrophysiol. 2011;4:543-549

PIC Model



Huizar JF et al. Circ Arrhythm Electrophysiol. 2011;4:543-549

Critical Appraisal

- Animal model study
- Pacing site: RV apex (NOT usual PVC site)

➔Model for RV apical pacing-induced HF rather than PIC

PIC: Mechanisms

- Altered Ca homeostasis
- Fibrosis

Left Ventricular Dyssynchrony Predicts the Cardiomyopathy Associated With Premature Ventricular Contractions

Tomos E. Walters, MD, PhD, Dolkun Rahmutula, MD, PhD, Judit Szilagyi, MD, Christina Alhede, MD, PhD, Richard Sievers, BS, Qizhi Fang, MD, Jeffrey Olgin, MD, Edward P. Gerstenfeld, MS, MD

ABSTRACT

BACKGROUND The pathophysiology of cardiomyopathy associated with premature ventricular contractions (PVCs) remains unclear.

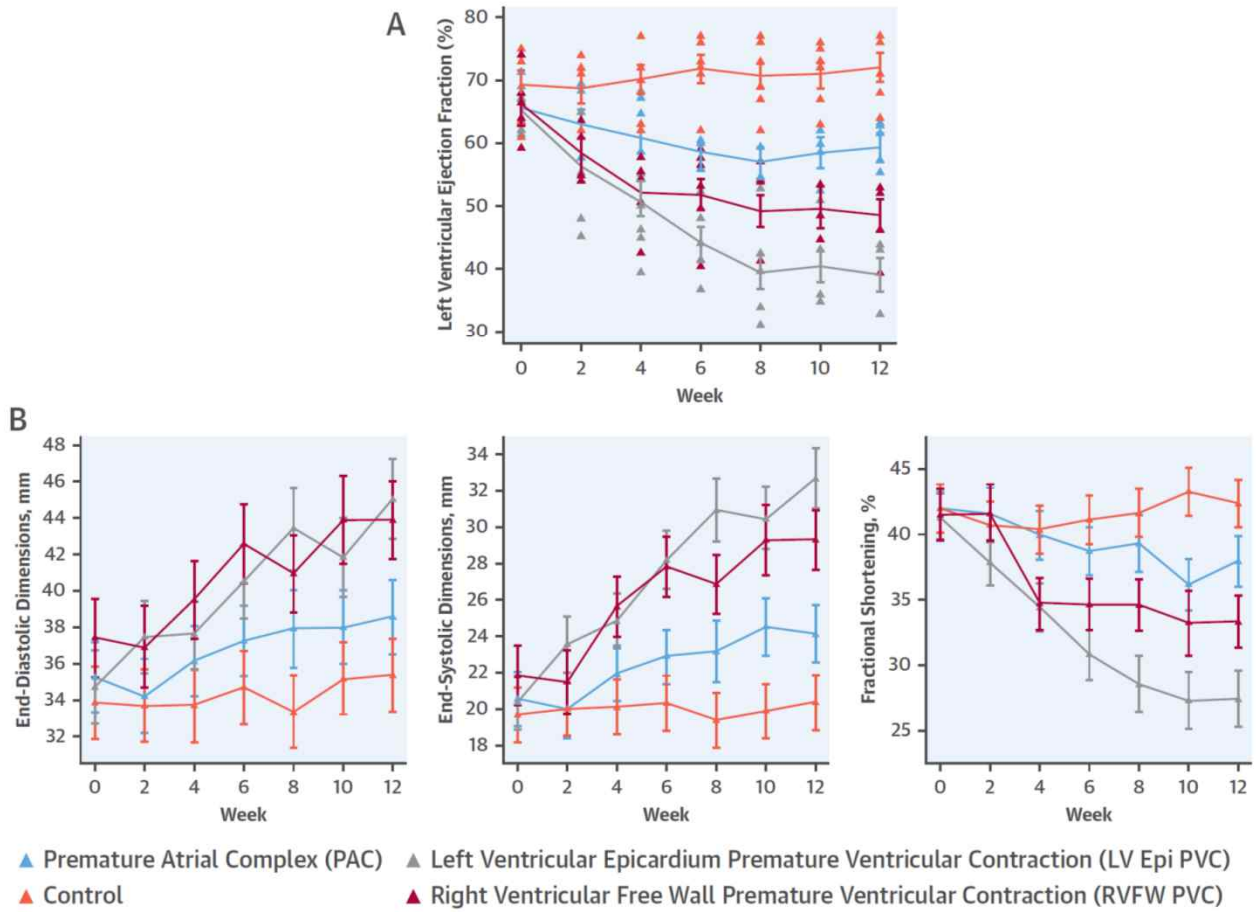
OBJECTIVES This study prospectively explored cardiomyopathy development in a swine model of paced ectopic beats.

METHODS A total of 35 swine underwent pacemaker implantation. A group exposed to paced bigeminy from the right ventricular apex (RVA) for 14 weeks (RVA PVC) ($n = 10$) were compared with a group exposed to regular pacing from the RVA at 140 beats/min (RV-140) ($n = 5$) and a control group ($n = 5$). To test the role of ectopic beat dyssynchrony, further groups were exposed for 12 weeks to bigeminy from the right ventricular free wall (RVFW PVC) ($n = 5$), the left ventricular epicardium (LV Epi PVC) ($n = 5$) or the right atrium (premature atrial complex) ($n = 5$).

RESULTS After 14 weeks, the mean left ventricular ejection fraction (LVEF) was significantly lower in the RVA PVC group than in the RV-140 or control groups ($p < 0.05$). LVEF declined significantly in the LV Epi PVC ($65.2 \pm 2.4\%$ to $39.7 \pm 3.0\%$; $p < 0.01$) and RVFW PVC ($66.1 \pm 2.6\%$ to $48.6 \pm 2.7\%$; $p < 0.01$) groups, with final LVEF significantly lower and ventricular fibrosis significantly higher in the LV Epi PVC group compared with all others ($p < 0.05$). Protein levels of pRyR2, NCX-1, CaMKII-α, and PLN were up-regulated and levels of SERCA2a were down-regulated in the LV Epi PVC group compared with the control group ($p < 0.05$). Longer ectopic beat QRS duration and greater LV dyssynchrony were significantly associated with larger declines in LV systolic function.

CONCLUSIONS In a swine model of paced ectopic beats, PVC-induced cardiomyopathy is phenotypically distinct from a tachycardia-induced cardiomyopathy. Cardiomyopathy severity is strongly associated with severity of the hemodynamic derangement associated with the paced ectopic beats, particularly the extent of LV dyssynchrony.
(J Am Coll Cardiol 2018;72:2870–82)

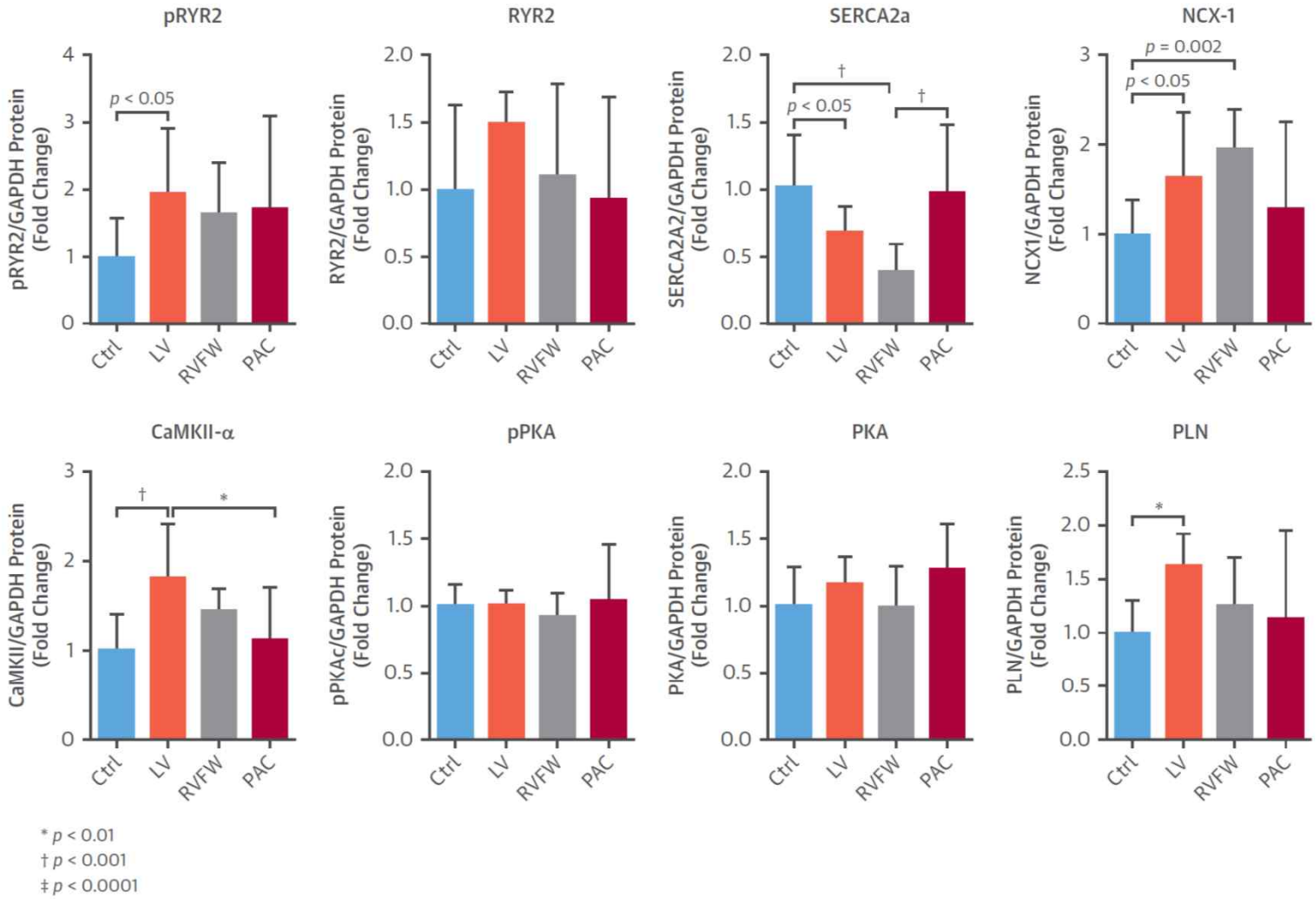
CENTRAL ILLUSTRATION **Change in Left Ventricular Systolic Function and Dimensions Over 12-Week Pacing Protocol in Study Phase 2**



Walters, T.E. et al. J Am Coll Cardiol. 2018;72(23):2870-82.

(A) Left ventricular (LV) systolic function determined from biweekly transthoracic echocardiograms. There was significant between-group divergence in left ventricular ejection fraction (LVEF). A significant decrease in LV systolic function was seen in both the right ventricular free wall (RVFW) premature ventricular contraction (PVC) and the LV epicardium (Epi) PVC groups, with a significantly lower LVEF value at 12 weeks in the LV Epi PVC group than in all other groups ($p < 0.05$). Raw data for each animal is presented, plus estimates generated by a linear mixed model, with **error bars** representing standard errors of the mean. **(B)** LV dimensions and fractional shortening from biweekly transthoracic echocardiograms. LV end-diastolic and end-systolic dimensions increased significantly, and fractional shortening fell significantly only in the LV Epi PVC and the RVFW PVC groups, with a significantly larger LV end-systolic dimension and a significantly smaller fractional shortening value at 12 weeks in the LV Epi PVC group than in all other animal groups. Estimates are generated by linear mixed models, with **error bars** representing standard errors of the mean.

FIGURE 7 Between-Group Differences in LV Levels of Proteins Involved in Cellular Calcium Metabolism in Study Phase 2



Protein levels of pRyR2, NCX-1, CaMKII-α, and PLN were all significantly upregulated in the LV Epi PVC group compared with the control group, whereas the level of SERCA2a was significantly down-regulated in both the LV Epi PVC and RVFW PVC groups. There was no significant difference in calcium handling protein levels between the LV Epi PVC group and the RVFW PVC group. Ctrl = control; LV = left ventricular; PAC = premature atrial complex; RVFW = right ventricular free wall.

Walters TE et al. J Am Coll Cardiol 2018;72:2870-2882

Cellular mechanism of premature ventricular contraction–induced cardiomyopathy

Yuhong Wang, PhD,[*] Jose M. Eltit, PhD,[*] Karoly Kaszala, MD, PhD, FHRS,[*†] Alex Tan, MD,[*†] Min Jiang, PhD,[*] Mei Zhang, PhD,[*] Gea-Ny Tseng, PhD, FAHA,[*] Jose F. Huizar, MD, FHRS[*†‡]

From the [*]Department of Physiology and Biophysics, Virginia Commonwealth University, [†]McGuire VA Medical Center, and [‡]Pauley Heart Center of Virginia Commonwealth University, Richmond, Virginia.

- Excitation-contraction coupling impairment
  - Reduction in Ca channel protein (Cav1.2) expression and I_{CaL} current density
  - Misalignment between Cav1.2 and RyR2

- Prolongation and marked beat-to-beat variation in APD, as well as decreased outward and inward (L-type calcium) currents ➔ increased repolarization heterogeneity

Wang Y et al. Heart Rhythm2014;11:2064–2072

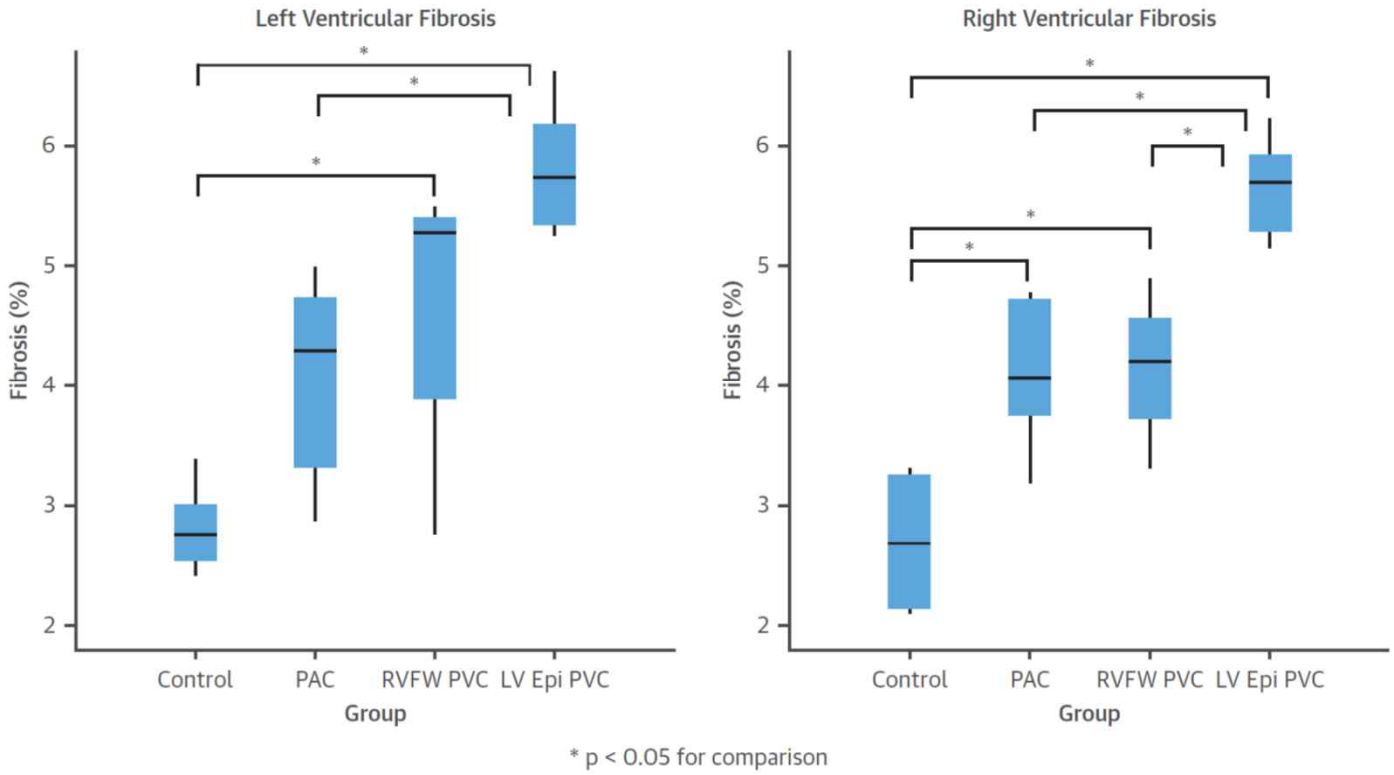
Altered Ca homeostasis in CHF

- Decrease of SR $[Ca]^{2+}$ stores
- Decrease of SR $[Ca]^{2+}$ sequestration
- Impaired $[Ca]^{2+}_i$ transients

Luo M et al. Circ Res 2013;113:690–708
Marks AR. J Clin Invest 2013;123:46–52

Mechanism: Fibrosis

- Biventricular fibrosis was observed in paced bigeminal swine model with PIC when compared with control animals, and the fibrosis was more pronounced with pacing from the epicardium as compared to other sites.



Walters TE et al. J Am Coll Cardiol 2018;72:2870-2882

Mechanism: Fibrosis

- In a canine study, no fibrosis was observed when a similar pacing protocol was carried out over a similar time period.

- It is possible that the development of fibrosis is a time-dependent process that might differ from species to species.

- The time line of development of PIC in humans is longer than what was observed in the animal studies.

Summary

- PIC is an often treatable and reversible condition

- Mechanisms: not clear
  - Altered Ca homeostasis
  - Fibrosis

- Treatment of Pts with frequent PVC
  - Try to find out Pts at risk of PIC

Contributors

SNU EP Faculty

Seil Oh, MD, PhD
Eue-Keun Choi, MD, PhD
Il-Young Oh, MD, PhD
Youngjin Cho, MD
Myung-jin Cha, MD
Woo-Hyun Lim, MD
Ji Hyun Lee, MD
So-Ryoung Lee, MD

EP Fellow (2019)

Euijae Lee, MD

Sejong General Hospital

Wonseok Choe, MD