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Impact of Ventricular Ectopic Burden in a Premature Ventricular Contraction-induced Cardiomyopathy Animal Model

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Abstract

Background—Frequent premature ventricular contractions (PVC) have been associated with PVC-induced cardiomyopathy (CM) in some patients.

Objective—Understand the cardiac consequences of different PVC burden and minimum burden required to induce LV dysfunction.

Methods—RV apical PVCs at a coupling interval of 240ms were introduced at different PVC burden in 9 mongrel canines. A stepwise increase in PVC burden was implemented every 8 weeks from 0% (baseline), 7%, 14%, 25%, 33% to 50% using our premature pacing algorithm. Echocardiogram and 24-hr Holter were obtained at 4- and 8-week period at each PVC burden with a single blinded reader assessing all echocardiographic parameters including speckle tracking imaging (GE EchoPAC). CM was defined as LVEF < 50% or a decrease >10% points. IL-6 and pro-BNP levels were obtained at the end of each PVC burden.

Results—LVEF±SD (mean heart rate ± SD) for 0%, 7%, 14%, 33%, and 50% at 8 weeks for each PVC burden were 57±2.9% (85±13bpm); 54.4±3% (81±10bpm); 53.3±5% (77±12bpm); 51.1±4.2% (79±14bpm); 47.7±3.8% (80±14bpm); 44.7±1.9% (157±43bpm). PVC-induced CM was present in 11.1%, 44.4%, and 100% of animals with 25%, 33% and 50% PVC burden, respectively. E/A ratio and radial strain decreased while LA size increased beyond 33% PVC burden. No changes in pro-BNP and IL-6 levels were noted at any PVC burden.

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Conclusion—LV systolic function (LVEF, and radial strain) declined linearly as PVC burden increased. PVC-induced CM developed in some canines with 25% and 33% PVC burden, but developed in all animals with 50% PVC burden.

Keywords

Premature ventricular contractions; LV dysfunction; cardiomyopathy; PVC-induced Cardiomyopathy

Introduction

Frequent premature ventricular contractions (PVCs) have been associated with an increased risk of sudden cardiac death (SCD) and have been identified as a reversible cause of non-ischemic cardiomyopathy (CM), referred to as a PVC-induced CM[1-5]. Although, radiofrequency ablation and antiarrhythmic drugs are accepted strategies to reverse LV dysfunction due to PVCs[1, 3-7], the minimum burden, origin (LV, RV, outflow, endocardial, epicardial) and coupling interval of PVCs required to impair LV function are unknown[8]. The cardiac consequences of different PVC burdens and the minimum burden required to induce LV dysfunction or PVC-induced CM are important but challenging questions to answer because of significant PVC variability in the clinical setting[9].

Using our unique premature pacing algorithm[2], we sought to understand the progression of echocardiographic changes associated with incremental PVC burden (7%, 14%, 25%, 33% and 50% PVC burden) and determine the minimum PVC burden required to induce LV systolic dysfunction in our canine model.

Methods

A left thoracotomy was performed in 9 canines to implant an RV apical epicardial pacing lead and modified experimental device (St. Jude Medical, Inc., Sylamar, CA) with our premature pacing algorithm[2]. All animals participated in a baseline 4 to 6-week observation period (without PVCs, disabled premature pacing algorithm) during which they had a baseline echocardiogram at the beginning and end of this period. In addition, 24-hour Holter, pro-BNP and IL-6 serum levels were obtained at the end of baseline period. After this baseline period, all 9 animals were followed by five 8-week periods in which the PVC burden was increased in a stepwise fashion, from 7%, 14%, 25%, 33% and 50%, without interruption of PVCs between different burdens (Supplemental Figure 1). All PVCs originated from the RV apex with a coupling interval of 240ms, regardless of burden.

Holter monitors

A 24-hr Holter (GE SEER Light) was obtained within the 8-week period of each PVC burden to assess average heart rate, PVC burden and PVC count using MARS GE software (General Electric, Fairfield, CT, USA).

Echocardiographic evaluation

Echocardiograms (GE Vivid 7) were repeated at 4 and 8 weeks after initiation of each PVC increment. PVC burden protocol was concluded after completion of all 5 different PVC burdens (46 weeks total). To assess the chronic effects of frequent PVCs, the echocardiogram was performed at least 10 minutes after disabling the pacing algorithm (PVCs absent). PVC-induced CM was defined as a LVEF < 50% or LVEF drop >10% points.

Echocardiographic images were obtained (5MHz probe GE Vivid-7, Vingmed General Electric, Fairfield, CT, USA) following the American Society of Echocardiography guidelines[10]. LV function was assessed by LVEF (Simpson's formula), fractional shortening (FS), LV endsystolic and diastolic dimensions (LVESD, LVEDD), LV thickness, left atrial (LA) size, mitral valve (MV) function, and LV compliance (E/A ratio)[10]. Abnormal LV compliance (diastolic dysfunction) was defined as E/A ratio < 1[11]. Speckle-tracking analysis was performed offline with an EchoPAC workstation (General Electric, USA). A short-axis (mid LV at level of papillary muscles) echocardiographic view was used to obtain radial and circumferential strain. Finally, LV dyssynchrony was assessed by the dispersion of QRS-to-peak strain (ms) between 6 different LV segments (earliest – last QRS-to-peak strain). All echocardiographic analysis was performed by a single reader blinded to the different PVC burdens.

Pro-Brain natriuretic peptide (BNP) and Interleukin-6 (IL-6) levels

Blood samples were obtained at baseline and at the end of each 8-week period for each incremental step of PVC burden without interruption of PVCs (premature pacing algorithm remained active). Blood tubes were spun to obtain serum and plasma, immediately stored at −73°C until the sample was analyzed. Pro-BNP and IL-6 levels were measured using canine-specific enzyme-linked immunosorbent assays (ELISA) (MyBioSource, Inc.). Samples were analyzed in at least triplicate (n=3-6) in a 96 well plate format and absorbance data collected via plate reader (Tecan).

All procedures were approved by the McGuire Institutional Animal Care and Use Committee (IACUC) in accordance with USDA Animal Welfare Act Regulations and Standards.

Statistical analysis

All data is reported as the mean + SD. The actual percentage of PVCs was calculated using a repeated measures logistic regression model. This method controls for any intra-individual variability found in the results. The estimated proportion of PVCs and associated 95% confidence intervals (CIs) were calculated for each PVC burden level. The mean number of PVCs per day and heart rate was measured with a repeated measures ANOVA; associated 95% CIs were also calculated.

The change in LVEF between different PVC burdens was compared using repeated measures ANOVA. This model included a fixed effect for time, which had a unique PVC burden for each time point as well as a random effect to account for relationship within each

animal. Separate repeated measure ANOVA models were fit for each of the outcomes using the baseline and 8-week observation for each PVC burden level (Table 1). Using these models, each PVC burden level (7%, 14%, 25%, 33%, 50%) was compared to baseline (0%) at the Bonferroni-corrected Type-I error rate of 0.01 (0.05/5). No formal analysis was made for the degree of mitral regurgitation (MR) due to numerical convergence issues; summaries of the different degrees of MR for each PVC burden level were presented instead. Statistical analysis was performed using SAS/STAT® Software (SAS Institute, Inc. Cary, NC).

Results

24-hour Holter

PVC burden and count, and mean heart rate (HR) are summarized in Table 1. Representative ECGs of different PVC burdens in a single animal are shown in Supplemental Figure 2. The actual PVC burden was similar to the programmed or desired PVC burden. The HR appeared to be fairly consistent across the different PVC burden, except for the 50% PVC burden, where the HR increased dramatically.

Echocardiogram

PVC-induced CM (drop on LVEF > 10% points or LVEF < 50%) was absent in all animals after 8-week exposure of 7% and 14% PVC burden. PVC-induced CM was present in 1/9 (11.1%), 4/9 (44%), and 9/9 (100%) of animals with 25%, 33% and 50% PVC burden, respectively. For the same PVC burden, severity of PVC-induced CM did not change significantly between 4 and 8 weeks.

The mean 8-week echocardiographic parameters are displayed in Table 2. The change in LVEF ($P<0.001$), LVEDD ($P<0.001$), E/A ratio ($P=0.018$), LA size ($P=0.011$), radial and circumferential strain ($P<0.001$ and $P=0.025$, respectively) demonstrated significant differences between different PVC burden levels. No differences were observed between the 4- and 8-week observation points for any of the echocardiographic parameters ($P>0.05$, Supplemental Table 1). As the predicted PVC burden increased, changes in the LVEF, LVEDD, E/A ratio, LA size and radial strain were observed (Figure 1 and 2). Compared to baseline, significant differences in the LVEF and LVEDD were observed starting at 14% PVC and continued throughout subsequent PVC burden until 50%. A similar pattern was observed for E/A ratio, LA size, and radial stain, but the significant differences began at 33% PVC burden. There was no significant difference in LV circumferential strain until PVC burden >33%. No statistical differences in LV hypertrophy (posterior and septal wall thickness) and LV dyssynchrony (QRS-to-peak radial strain) were observed between different PVC burdens.

Even though no statistical test was performed assessing the relationship between PVC burden and MR severity, a clear relationship is apparent. At baseline, a third (N=3, 33%) of the animals had trace MR, with the remainder being rated ‘None’ (N=6, 67%). After exposure to a PVC burden of 25%, all animals (N=9, 100%) had trace MR. At 50% PVC burden, four of the animals (N=4, 43%) had 1+ MR with the remainder (N=5, 57%) having trace MR, demonstrating a clear increase in MR (Table 2).

Biomarkers

Serum IL-6 levels did not change significantly between 0, 7, 14, 25, 33 and 50% PVC burden (22.6 ± 8 , 23.8 ± 11, 24.0 ± 9, 21.4 ± 11, 22.7 ± 7 and 21.0 ± 8 pg/mL, respectively), whereas pro-BNP levels remained below clinically significant levels without a clear correlation with PVC burden (87.4 ± 68, 33.4 ± 29, 33.6 ± 31, 60.4 ± 49, 93.4 ± 100.1 and 35.9 ± 27 pg/mL at 0, 7, 14, 25, 33 and 50% PVC, respectively).

Discussion

This is the first animal study to assess the cardiac consequences of different PVC burdens (from 7 to 50%) of chronic (>2 months) RV apical PVCs at a fixed level of prematurity (240ms coupling interval) in otherwise structurally normal canine hearts. We demonstrated that: 1) LV function declines linearly as PVC burden increases (Figure 1) ; 2) a minimum and a mean PVC burden of 25% and 33% is required to induce CM (defined as LVEF < 50% or LVEF drop >10% points) as this occurred in 1 out of 9 animals and 4 out of 9 animals, respectively, compared with all animals with 50% PVC burden; 3) statistical reduction in LVEF and increase in LVEDD were noted with as little as 14% PVC burden despite a preserved LV systolic function (LVEF >50%, Figure 1 and 2); 4) LV systolic function (assessed by radial strain) decreases with as little as 7% PVC burden even with a preserved LV ejection fraction, 5) LA size increases while E/A ratio decreases with PVC burden greater than 33% (Table 2).

Significant limitations exist to identify a mean or minimal PVC burden in clinical studies, due to large variability of PVC origin and coupling interval between patients. A small retrospective clinical study[7] suggested that a mean PVC burden of 24% (assessed by 24-hour Holters) is required to develop PVC-induced CM (LVEF < 50%), while, almost no patients developed CM with a 10% or lower PVC burden. However, assessment of PVC burden based on a single 24-hour Holter monitor is an inaccurate measure of true long-term PVC burden because of a high variability of spontaneous PVC frequencies over extended periods of time[9]. The difference in the minimum and mean PVC burden required to induce CM between published retrospective clinical studies and our canine study could be explained by: 1) methodology (retrospective vs. prospective study), 2) difference in PVC location or coupling intervals, 3) underestimation of PVC burden by a single 24-hour Holter, and/or 4) inter-species variability in susceptibility to PVC-induced cardiomyopathy. Therefore, an animal model with a constant PVC burden is key to determine the relationship between PVC burden and development of PVC-induced CM.

Similar to clinical data[1, 4, 6, 7, 12], some animals appear to be more susceptible to develop PVC-induced CM, as not all animals develop LV dysfunction even at a 25 and 33% PVC burden despite identical origin and coupling interval. This individual susceptibility to PVC exposure suggests the presence of a genotype or molecular phenotype that predisposes to the development of this CM. This molecular phenotype could be associated with differences in junctophylin-2 (scaffolding protein known to regulate the interaction between the Ryanodine receptor and L-type calcium channel) and L-type Calcium channel found to be altered in PVC-induced CM[13].

Our study revealed that LV systolic function deteriorates as the PVC burden increases. A clinical study by Wijnmaalen et. al.[14] showed that subtle LV systolic dysfunction associated with frequent PVCs can be identified if assessed by speckle-tracking imaging even when LV ejection fraction is considered preserved (LVEF > 50%). They supported this finding by showing that radial, circumferential and longitudinal strain normalized after elimination of chronic PVCs. This data is consistent with our animal study, where all animals had an early decrease in radial strain prior to the development of PVC-induced CM (Table 2 and Figure 2, Supplemental Figures 3-8). Thus, our study supports that radial strain imaging can be used to detect a "pre-clinical" stage of PVC-induced CM or predict the development of PVC-induced CM when LVEF is above 50%. Moreover, assessment of LV mechanics using speckle-tracking imaging (dispersion of QRS-to peak radial strain on 6 different LV segments) showed a trend towards increased LV dyssynchrony as PVC burden is increased (Table 2).

To our knowledge, only one small clinical study suggests improvement in LA and LV diastolic dysfunction after radiofrequency ablation of PVCs[15]. Our experimental study suggests that mild LA enlargement and LV diastolic dysfunction (changes in E/A ratio) could be associated with states of high PVC burden (> 33%, Figure 2). In contrast, mitral regurgitation has been previously reported in patients with PVC-induced CM[4, 8]. Future clinical and animal studies are required to better understand the effects of PVCs on diastolic function and LA dimensions. For now, we can only speculate that LA dilatation is unlikely related to the subtle changes in MR alone, but rather the combination of MR, AV dissociation and diastolic dysfunction.

Surprisingly, pro-BNP levels did not increase as the PVC burden increased and cardiomyopathy developed. However, blood samples were only obtained while PVCs were present (premature pacing algorithm enabled). We speculate that post-extrasystolic potentiation during PVCs maintain a stable hemodynamic state that prevents BNP elevation as demonstrated in prior canine's studies of post-extrasystolic potentiation where paired pacing (analogous to ventricular bigeminy) did not compromise cardiac output[16-18]. This was also clinically apparent since these animals did not appear to develop clinical signs of heart failure. The absence of IL-6 changes confirms that PVC-induced CM is not mediated by an inflammatory response as first reported in histopathological analysis[2].

Mechanism of PVC-induced Cardiomyopathy

Our study provides some insight into the mechanism of PVC-induced CM, since 44% of the animals developed CM (LVEF <50%) when exposed to 33% PVC burden despite a mean heart rate of 82 bpm (Table 1). Furthermore, a gradual and linear decline in LVEF and radial strain at PVC burden from 7 to 33% PVC burden suggests that tachycardia plays little or no role in the development of PVC-induced CM.

The reason for the significant increase in HR between 33 and 50% PVC burden remains elusive. We can only speculate that this is not only due to the increase in PVC burden but also changes in autonomic tone due to a chronic and cumulative exposure to frequent PVCs. Even though we cannot rule out tachycardia as a contributing mechanism at 50% PVC burden in this series of animals (mean heart rate 157 ± 43 bpm, we believe this is unlikely

since: 1) 4 out of the 9 animals had a heart rate between 103 – 126 bpm when exposed to 50% PVC burden yet they all developed CM (mean LVEF of 45%), 2) canine models of tachy-induced cardiomyopathy have been described with HR > 180 bpm[19, 20], and 3) our original manuscript where our animals were exposed to only 3-month PVC (bigeminal pattern) with a mean heart rate of 130 ± 13 bpm developed LV dysfunction of a similar magnitude.

Besides PVC burden, small retrospective clinical studies highlighted other PVC features that may potentially contribute to the development of cardiomyopathy. In some studies, QRS duration and epicardial origin may be correlated with the development of PVC-induced CM[7, 21, 22], while in others, the impact of PVC origin and coupling interval (prematurity) remains poorly understood[12, 23-25]. The discrepancy may be related to limited sampling duration for PVCs which fails to capture true PVC burden and/or location. Future prospective clinical studies and animal models are needed to clarify the contribution of these PVC features to the development of PVC-induced CM.

Limitations

1. Due to the incremental PVC burden protocol, we cannot exclude the possibility that the development of PVC-induced CM was related to the cumulative effect of PVCs frequency. However, the severity of PVC-induced CM at a 50% PVC burden (after gradual stepwise increase in PVC burden) was no different from our original published model with a 3-month single burden PVC exposure. The latter also demonstrated LV dysfunction of a similar magnitude. This suggests that there was little or no cumulative effect of PVCs. The strength of this protocol is that each animal served as its own control to assess the effects of different PVC burden on LV function and development of PVC-induced CM.

2. Exposure to each PVC burden was for a duration of 8 weeks. Based on our initial report[2], the effect of chronic exposure to PVCs in canines appears to plateau at 8 weeks. Thus, we postulate an insignificant or no further deterioration of LV function occurs beyond 8 weeks. In contrast to clinical data suggesting the need of prolonged PVC exposure to induce CM[26], our PVC canine model develops CM with a shorter but consistent (uninterrupted) 8-week PVC burden. We speculate that longer periods of PVC exposure are required to induce CM in humans due to variability in PVC burden[9, 27].

3. Ventricular ectopy was limited only to the RV apex and may not apply to PVCs of other origins, such as LV and RVOT. Yet, our findings are relevant since one of the largest case series (40+ patients) of PVC-induced CM reported similar number of cases between different PVC origins[24], as well as unifocal or multifocal PVCs. Similarly, another study reported no difference in the hazard ratio for the development of PVCs between LV, RVOT and non-RVOT PVCs, while 70% of PVC-induced CM was associated with non-RVOT PVCs[7].

4. Pro-BNP levels were obtained during active ventricular ectopy, in contrast to echocardiographic images which were obtained 5-to-10 minutes after premature pacing algorithm was disabled. Thus, it is possible that post-extrasystolic

potentiation maintained sufficient hemodynamic stability to prevent significant release or change in BNP levels.

5. This study was performed only in structurally normal hearts. The minimum PVC burden required to deteriorate LV systolic function in subjects with preexisting structural heart disease remains unclear.

6. All animals were between 1-2 years old. Thus, it is unclear if the same PVC burden at older ages would have a different impact on the development of PVC-induced cardiomyopathy.

Conclusions

LV function declined linearly as PVC burden increased. PVC-induced CM (LVEF < 50% or LVEF drop >10% points) was present in a few canines with 25% and 33% PVC burden without a difference in mean heart rate, while PVC-induced CM was present in all animals with 50% PVC burden. However, subtle LV systolic dysfunction can be demonstrated by a decrease in LV ejection fraction and radial strain strain even at PVC burdens below 25%. Our study supports that speckle-tracking imaging can be used to assess early stages of PVC-induced CM or predict the development of PVC-induced CM when LVEF is above 50%. Moreover, a decrease in E/A ratio suggests that LV diastolic dysfunction also develops as PVC burden increases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

Tan A – Research support from Boston Scientific Corp (BS). and Biotronik, Inc. (BTK); Hu Y – None; Potfay J – None; Kaszala K – Research support from Medtronic, Inc (MDT); Howren M – None; Sima A – None; Shultz M – None; Koneru JN – Honoraria from MDT, BTK, and Atricure; Ellenbogen KA – Research support from BS, Biosense Webster (BW), MDT, St. Jude Medical (SJM), NIH, Consultant for BS, SJM, Atricure, Medtronic, Honoraria from MDT, BS, BTK, BW and Atricure; Huizar JF – Research support from BS, BTK and SJM.

Abbreviations

PVCs	Premature ventricular contractions
SCD	Sudden cardiac death

CM	Cardiomyopathy
LVEF	LV ejection fraction
FS	Fractional shortening
LVESD	LV end-systolic dimension
LVEDD	LV end-diastolic dimension
LA	Left atria
MV	Mitral valve
MR	Mitral regurgitation
PW	Posterior wall
SW	Septal wall
HR	Heart rate
Bpm	beats per minute
CIs	Confidence intervals

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Clinical Perspectives

This study determined for the first time, the cardiac consequences of different PVC burdens (from 7 to 50%) in otherwise structurally normal canine hearts. We demonstrated that LV systolic function declined linearly as PVC burden increased. The minimum and mean PVC burden required to induced cardiomyopathy (LVEF < 50% or LVEF drop >10% points) was 25% and 33%, respectively, while all animals developed a cardiomyopathy (CM) when exposed to 50% burden. Additionally, changes in LV radial by speckle tracking echocardiography were detectable with as little as 7% PVC burden and prior to the development of PVC-induced CM. Thus, LV strain may represent a new method of detecting pre-clinical stages of PVC-induced CM, allowing us to identify patients with frequent PVCs and preserved LVEF at imminent risk of developing a CM. Finally, mild LA enlargement and LV diastolic dysfunction (changes in E/A ratio) may be present in high PVC burden states (>33%, trigeminy) suggesting that LV diastolic dysfunction could contribute to heart failure in patients with frequent PVCs.

While, future randomized clinical studies are needed to compare outcomes between different treatment strategies in PVC-induced cardiomyopathy, these studies should include assessments of LV diastolic dysfunction and LA size after PVC suppression. Moreover, additional studies are also needed in patients with frequent PVCs to validate the use of LV strain to identify subclinical or early stages of PVC-induced CM.

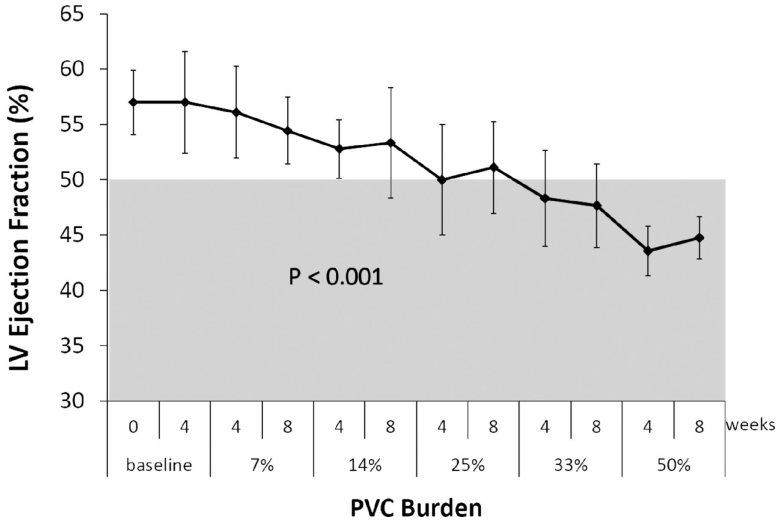

Figure 1.

Progression of LV ejection fraction after 4 and 8 weeks of a progressive incremental PVC burden starting from 0% (baseline) to 7, 14, 24, 33 and 50%. *P value, repeated measures one-way ANOVA.*

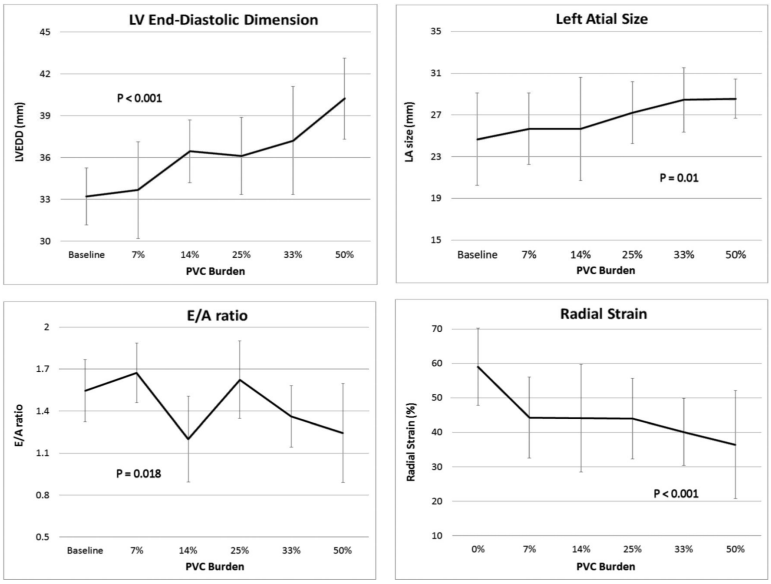

Figure 2.

Estimated means of LVEDD, LA size, E/A ratio, and strain that showed a significant change between PVC burden levels (0%, 7%, 14%, 25%, 33% and 50%). *P value, repeated measures one-way ANOVA.* Details are given in Table 2.

Table 1

Holter data at each predicted PVC burden.

	Anticipated PVC burden					
Holter Data[a]	**0%**	**7%**	**14%**	**25%**	**33%**	**50%**
Actual PVC Burden (%)	0.018 (0.016, 0.021)	7.8 (7.5, 8.1)	14.9 (14.5, 15.4)	25.2 (24.5,25.9)	32.8 (32.0, 33.7)	49.5 (28.6, 50.5)
#PVC / day	22 (0, 64)	9,000 (7K, 11K)	17,000 (14K, 19K)	33.000 (30K, 36K)	45,000 (42K, 48K)	76,000 (71K, 82K)
Heart Rate (bpm)	85 (71, 99)	81 (67, 95)	77 (62, 91)	79 (65, 93)	82 (67, 96)	157 (143, 171)

Estimated percentages (Actual PVC Burden) and means (Number of PVCs per day and heart rate) over the predicted PVC burden levels. #PVC/day = Number of PVCs per day.

K Estimates are given in the thousands (×1000).

Table 2

Echocardiographic parameters (mean ± SD) after 8 weeks for each PVC burden (4-week parameters can be seen in Supplemental Table 1).

	Baseline	7%	14%	25%	33%	50%	P Value†
LVEF (%)	57 ± 2.9	54.4 ± 3.0‡	53.3 ± 5.0‡	51.1 ± 4.2‡	47.7 ± 3.8‡	44.8 ± 1.9‡	<0.001
FS (%)	33.1 ± 4.5	30.0 ± 4.0	30.9 ± 4.1	29.0 ± 4.8‡	25.7 ± 4.2‡	24.3 ± 3.0‡	<0.001
LVEDD (mm)	32.7 ± 2.6	33.7 ± 3.5‡	36.4 ± 2.2‡	36.1 ± 2.8‡	37.2 ± 3.9‡	40.2 ± 2.9‡	<0.001
LA Size (mm)	24.6 ± 3.0	25.7 ± 3.4	25.7 ± 4.9	27.2 ± 2.9	28.4 ± 3.1‡	28.6 ± 1.9‡	0.011
PW (mm)	9.1 ± 1.1	9.8 ± 1.3	9.8 ± 1.1	9.2 ± 1.0	9.1 ± 1.2	9.3 ± 1.3	NS
SW (mm)	10.4 ± 1.3	10.3 ± 0.9	10.0 ± 1.1	9.7 ± 0.7	9.9 ± 1.1	9.3 ± 0.7	NS
E/A ratio	1.7 ± 0.3	1.7 ± 0.2	1.2 ± 0.3	1.6 ± 0.3	1.4 ± 0.2‡	1.2 ± 0.4‡	0.018
MR grade	0 – trace	0 – trace	0 – trace	Trace	Trace - 1+	Trace - 1+	-
Radial strain	59 ± 11.2	44.3 ± 11.8‡	44.1 ± 15.6‡	44 ± 11.7‡	40.1 ± 9.7‡	36.4 ± 15.7‡	<0.001
Circumf. Strain	−18.1 ± 9	−16.9 ± 4.7	−18.4 ± 5.7	−15.6 ± 7.3	−16.2 ± 5.3	−13.8 ± 6.7‡	0.025
QRS-to-peak strain	32.0 ± 21.5	39.1 ± 34.7	47.8 ± 34.3	46.2 ± 28.1	69.0 ± 47.3	66.2 ± 41.6	NS

P value, repeated measures one-way ANOVA;

LVEDD, LV end-diastolic dimension; PW, posterior wall thickness; SW, septal wall thickness; MR, mitral regurgitation (grade 0 – 3+); Circumf, circumferential.

†P-values correspond to a test that at least one of the means differs from another.

‡*P<0.01* when compared to baseline (0%).