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Decay of postextrasystolic potentiation in the left and right ventricles of intact canine hearts

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Abstract— **Intracellular regulation of myocardial Ca^{2+} has long been of interest to physiologists. The force-interval relationship provides a phenomenological approach that permits insight into aspects of calcium regulation. The response to an extrasystole is a potentiation in contractile force and the recovery in contractile force is described by the recirculation fraction (RF). The RF provides a gross estimation of calcium uptake by sarcoplasmic reticulum (SR), leading to myocardial relaxation. The current study focused on the relationship of right (RV) and left ventricular (LV) RF in canines under several contractile states. Anesthetized canines (n = 5) were catheterized for RV and LV pressure measurements. dP/dt_{max} for the RV and LV was calculated for three baseline beats, one extrasystole and the first five postextrasystolic beats. The relationship between the LV dP/dt_{max} and RV dP/dt_{max} for all of the mentioned beats was then examined. Contractility was increased with calcium chloride and extrasystoles were delivered. Once cardiac function returned to a baseline level, contractility was reduced by increasing the concentration of isoflurane and the evaluation repeated. All ventricular contractions were controlled by RA pacing to maintain intrinsic conduction. A strong linear relationship between RV and LV dP/dt_{max} ($r = 0.94 \pm .06$) existed for most canine's contractile states. These results build on findings in isolated hearts and demonstrate that biventricular response to extrasystoles and subsequent contractile recovery is both linear and correlated, suggesting that intracellular calcium regulation in a given heart across contractile state is static.**

I. Introduction

THE force-interval relationship measures the ventricular response to a change in the interval between beats. An acute change in the interval produces an extrasystolic beat that loads the sarcoplasmic reticulum (SR) with Ca^{2+} [1]. Following the extrasystolic beat is a potentiated beat that decays monoexponentially with subsequent beats to a steady-state value. Research has excluded the effects of ventricular filling and other loading conditions from contributing to the decay [2, 3] as well as to postextrasystolic potentiation (PESP) [4-7]. The decay is representative of the recirculation fraction (RF)—the proportion of intracellular Ca^{2+} sequestered by the SR. LV PESP and its decay has been well established [8-13] but there is limited research into the RV and biventricular responses of the RF. Burkhoff [14] has shown the relationship between right ventricular (RV) and left ventricular (LV) force-interval curves to be linear at different heart rates. This finding demonstrated that despite the different geometries of the ventricles, the response across ventricles was similar. PESP has been explored in the RV [15] and in both ventricles during spontaneous ventricular ectopy [16]. The current study expands these findings by examining the LV and RV systolic relationship during the steady-state, extrasystole, PESP, and recovery beats across a wide range of contractile states. This approach may be useful for evaluating the impact of changes in LV or RV function in various disease states.

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II. Methods

A. Data Collection

Following a 30-minute stabilization period, the canines were right atrially (RA) paced at 110-130 bpm. To ensure consistent capture during pacing, 110-130 bpm were the lowest rates employed for this study. In order to minimize respiratory sinus arrhythmias, each train of beats was initiated when the respirator was at full expiration The subjects received eight steady-state pulses (S1s) followed by a single S2 (extrasystole) and five S3s (postextrasystoles) (Figure 1). The shortest S2 to elicit a mechanical response was determined and the process was repeated with such that each subsequent S2 was increased in cycle length by 20 ms with each train. Once the extrasystolic interval (ESI) reached the steady-state heart rate minus 100 ms, it was increased by 10 ms until escape beats occurred. The RF was generated by delivering an extra systole (force-interval relationship) followed by RA pacing at the baseline rate.

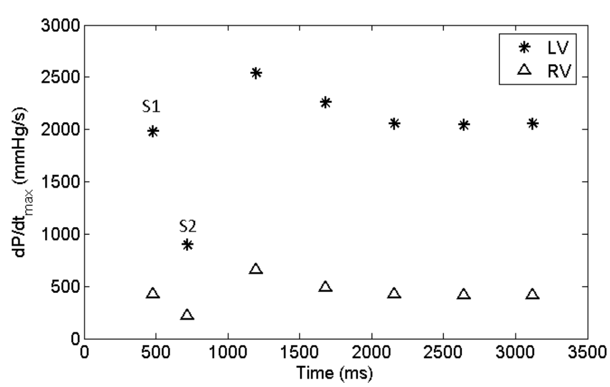

Fig. 1. An example of the response to an extrasystole. The first beat is the steady-state value (S1), then extrasystole (S2), and following potentiation and decay.

B. Data Analysis

The RF was determined for each ventricle by calculating the slope of $dP/dt_{max}(n+1)$ vs. $dP/dt_{max}(n)$ using linear regression where n is the beat number. Statistical analysis on the RV LV dP/dt_{max} relationship was performed on RV dP/dt_{max} using a general linear model. LV dP/dt_{max} was selected as a covariate and the subjects were the random variable whereas the contractile state was fixed.

III. Results

All pressure data were collected from the shortest ESI that elicited a ventricular response. The ESI varied between contractile states and between canines from 240-300ms. The relationship between RV and LV dP/dt_{max} from the S1 through the fifth PESP beat for all contractile states is shown in Figure 2.

A. Hemodynamic Response to drug intervention

dP/dt_{max} was used as a contractility measure and the effect of the induced inotropic states on the RV and LV dP/dt_{max} values are described in Table I. There was a significant change in both RV ($p < .05$) and LV dP/dt_{max} ($p < .005$) for the isoflurane and calcium chloride interventions. The effects on end diastolic pressure (EDP) and end systolic pressure (ESP) taken at the different contractile states are also in Table I. Baseline LV ESP and RV EDP decreased significantly from the isoflurane values ($p < .05$). Calcium chloride increased LV ESP ($p < .05$) in all cases. There was good agreement for 13 of the 15 cases ($p < 0.05$) between RV and LV dP/dt_{max} S1-PESP recovering beats (Table II). The cases with poor correlations demonstrated an alternan behavior in RV recovery (Figure 3).

TABLE I
HEMODYNAMIC EFFECTS OF DRUG INTERVENTIONS

Subject	Baseline	Isoflurane	Calcium Chloride
LV dP/dt_{max} (mmHg/s)			
1	1394.0	896.2	2279.4
2	957.1	754.0	1979.9
3	1226.1	863.8	2295.4
4	1092.7	833	1685.35
5	1366	873.8	2518.2
RV dP/dt_{max} (mmHg/s)			
1	369.0	194.9	598.7
2	199.1	167.4	423.9
3	269.2	184.4	523.5
4	379.2	279.6	462.6
5	365.6	302.7	836.5
Pressure Parameters (mmHg)			
LVEDP	5.7 ± 4.1	6.7 ± 4.6	5.1 ± 5.4
LVESP	77.1 ± 10.7	*59.4 ± 7.5	*98.0 ± 21.3
RVEDP	6.3 ± 1	*7.6 ± 1.5	6.3 ± 2.3
RVESP	19.3 ± 8.4	14.5 ± 1.0	22.8 ± 14.8
ESI	272 ± 11	256 ± 17	276 ± 17

Mean Values for steady-state beats are given and pressure parameter include standard deviation.
*Significant change from baseline.

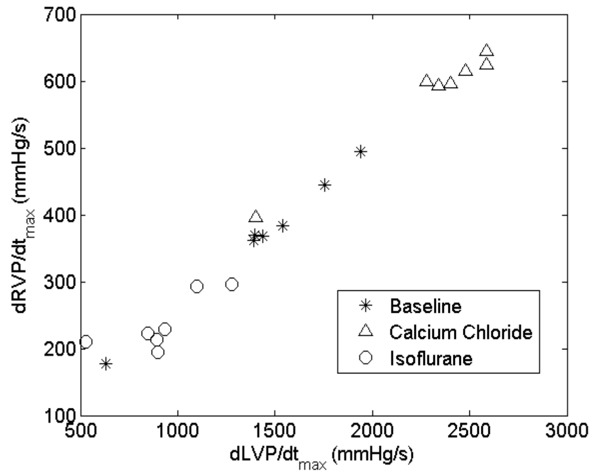

Fig. 2. The RV and LV response to an extrasystole at all contractile states for one canine.

B. Recirculation Fraction

The RF for each ventricle was calculated and the values are shown in Table III. No significant correlation existed between contractile states. RF greater than 100% reflects the previously mentioned alternans in the RV. The use of calcium chloride and isoflurane did not always cause the RF to increase or decrease from the baseline value.

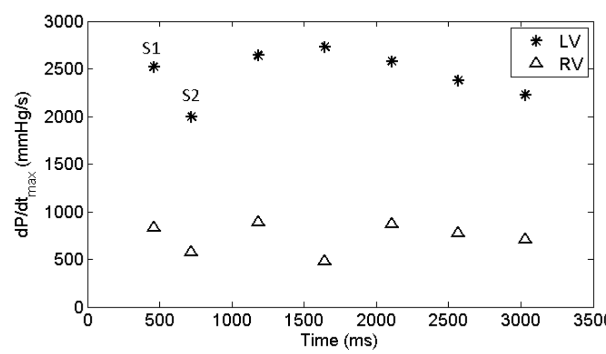

Fig. 3. The alternan response in the RV yields a low correlation between ventricles.

IV. Discussion

Comparison between RV and LV PESP decay and RF was investigated to determine the homogeneity of the RF and PESP decay in the ventricles. The PESP and the following decaying beats correlated well for most (13 of 15) cases. There was an oscillatory (alternan) behavior that was present in several cases and these findings have been reported in literature [17-21]. The lack of correlation in the two cases is due to a salient alternan effect in the RV.

Results from the statistical analysis for the RV LV dP/dt_{max} relationship showed that the contractile state was not a significant factor. Additionally, the relationship of RV dP/dt_{max} to both LV dP/dt_{max} and the subjects were both significant ($p < 0.001$). The similar RF values between ventricles further supports the linearity of the RV LV PESP

TABLE II
RV LV DP/DT$_{MAX}$

Subject	Baseline	Isoflurane	Calcium Chloride
1	0.998	0.785	0.991
2	0.922	*0.694	0.930
3	0.936	0.920	0.963
4	0.939	0.917	0.978
5	0.994	0.988	*0.227

The Correlation coefficients for all subjects and contractile states.
*Not significant

TABLE III
RECIRCULATION FRACTION

Subject	Baseline	Isoflurane	Calcium Chloride
Left Ventricle			
1	0.61	0.58	0.62
2	0.56	0.30	0.31
3	0.82	0.78	0.60
4	0.65	0.56	0.61
5	0.73	0.80	*-0.62
Right Ventricle			
1	0.71	0.60	*1.07
2	0.53	0.45	0.40
3	0.84	0.74	0.79
4	0.67	0.62	0.83
5	0.72	0.88	*1.21

*Alternans

decay relationship for all contractile states and its near identical response in both ventricles.

The RF has been shown to decrease in preparations with decrease ability to sequester calcium (i.e., heart failure) and increase in preparations where the contractile state has been increased. While the values did not move in the expected direction in each animal, the LV/RV relationship remained intact.

Future work would benefit from delineating the conditions that produce a lateralized alternan in PESP recovery to further clarify the biventricular relationship for PESP decay.

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