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Inotropic and lusitropic effects of incremental doses of dobutamine in dogs with right ventricular apical pacing-induced cardiac dysfunction

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Abstract

This study aimed to assess the effects of incremental doses of dobutamine on diastolic function in healthy and rapid ventricular apical pacing (RVAP)-induced cardiac dysfunction anesthetized dogs. Inotropic and lusitropic effects of dobutamine (2, 4, 8, and 12 μg kg^{-1} min^{-1}) were assessed through left ventricle (LV) pressure–volume relation and Doppler echocardiography in six female dogs before and after 8 weeks of RVAP. Peak rate of LV pressure fall ($-dP/dt_{min}$) improved with doses >4 μg kg^{-1} min^{-1} in healthy (4,490 ± 970 vs. 3,265 ± 471 mmHg/s, $p < 0.05$) and >8 μg kg^{-1} min^{-1} in RVAP dogs (3,385 ± 1,122 vs. 1,864 ± 849 mmHg/s, $p < 0.05$) while the time constant of relaxation (tau) reduced with doses >4 μg kg^{-1} min^{-1} in both groups (healthy: 24.0 ± 3.7 vs. 28.2 ± 4.9 ms; RVAP: 32.6 ± 8.5 vs. 37.5 ± 11.4 ms, $p < 0.05$) comparing with baseline. Indices of relaxation ($-dP/dt_{min}$ and tau) suggested preserved lusitropic response in contrast with markedly reduced indices of contractility in the RVAP group compared with healthy group at same infusion rates. Doppler echocardiography showed significant reduction of elastic recoil in failing hearts. The results of this study demonstrated maximal positive lusitropic effects of dobutamine at a dose of 8 μg kg^{-1} min^{-1} in ventricular pacing-induced cardiac dysfunction without further impairment of ventricular filling.

KEYWORDS
elastic recoil, heart failure, inotropy

1 | INTRODUCTION

Conventional right ventricular apical pacing (RVAP) alters the normal electrical and mechanical activation pattern in the left ventricle (LV) and impairs systolic and diastolic function (Sweeney & Prinzen, 2006). The major determinant of diastolic function is the potential energy storage through the twist motion of the LV during the systole and its conversion into untwist motion or elastic recoil toward their equilibrium position that results in ventricular filling during the succeeding early diastole (Bell, Fabian, & LeWinter, 1998; Solomon, Nikolic, Glantz, & Yellin, 1998). In this phase, the left atrioventricular pressure gradient (AVPG) increases and the transmural pressure gradient decreases producing a suction effect (Remme, Opdahl, & Smiseth, 2011; Udelson, Bacharach, Cannon, & Bonow, 1990). In the diastolic phase, pressure inside LV, left atrium, and pulmonary venous system is uniform, thus, an increase in LV pressure is transmitted to pulmonary vasculature resulting in congestion. Long-term RVAP alters LV filling and myocardial relaxation. The standard method used to assess these changes is the pressure–volume relationship (PVR; Bell et al., 2000). Previous studies suggested that administration of

catecholamines enhance diastolic function through improvement of elastic recoil independent of end-systolic volumes by increasing the equilibrium volume (Yotti et al., 2005). Lusitropic effects of catecholamines have been studied in patients with heart failure aiming at improving ventricular filling which provided a rationale for therapeutic approach to heart failure (HF; Parker, Landzberg, Bittl, Mirsky, & Colucci, 1991). Dobutamine is a β-adrenergic receptor (β-AR) agonist which increases intracellular levels of cAMP and calcium resulting in enhancement of cardiac output. However, it has been related to short- and long-term detrimental adverse effects of intracellular calcium overload (Blaustein & Gaasch, 1983; Pellikka, Nagueh, Elhendy, Kuehl, & Sawada, 2007; Tatsumi et al., 2010). In this study, effects of incremental doses of dobutamine were evaluated in healthy and rapid RVAP-induced heart failure dogs through invasive hemodynamic measurements (Kobayashi et al., 2008; Nagueh et al., 2016). Echocardiography variables were also assessed to provide a clinical method for determination of hemodynamic changes in failing hearts.

2 | MATERIALS AND METHODS

2.1 | Experimental model

This study was approved by Institutional Ethical for Animal Care and Use Committee of Tokyo University of Agriculture and Technology (approval process 25-23) and followed the Guide for the Care and Use of Laboratory Animals, National Research Council (2011).

Six female Beagles dogs, aging 18 ± 6 months and weighting 9.9 ± 0.94 kg, underwent cardiologic evaluation for exclusion of abnormalities before collecting baseline data (healthy control), and then, the dogs were instrumented with an externally programmable pacemaker for rapid RVAP.

2.2 | Study protocol

Left ventricle catheterization and Doppler echocardiography were performed simultaneously before (healthy group) the pacemaker lead implantation and after 8 weeks of rapid RVAP (heart failure group) under general anesthesia. The dogs were premedicated with midazolam (0.2 mg/kg) and butorphanol intravenously (0.2 mg/kg). After an intravenous injection of propofol (6.0 mg/kg), the dogs were intubated and positioned in left lateral recumbency under general anesthesia maintained with mechanical ventilation with 1.5% isoflurane end-tidal concentration in O_2. A period of 20 min was allowed for anesthesia stabilization prior to baseline data recording.

2.3 | Tachycardia-induced heart failure

A limited left-side thoracotomy in the fifth intercostal space was performed for pacemaker electrodes implantation at the right ventricular apical epicardium under general anesthesia ut supra. Bupivacaine 0.5% (0.5 ml) was injected locally for intercostal nerve blockage which was used to provide postoperative analgesia. A subcutaneous tunnel was created using blunt dissection for pacemaker leads connection with an externally programmable pacemaker.

A postoperative recovery period of 1 week with regular clinical evaluations was allowed before initiate RVAP. After complete recovery from the surgery, RVAP started at a heart rate 210 beat/min and maintained for 8 weeks. The heart rate (HR) was established according to the data of pacemaker implantation (twice the basal HR) in dogs in a clinical setting.

2.4 | Invasive hemodynamic measurements

Premedication and general anesthesia was performed as previously described. A 5-Fr catheter equipped with a micromanometer (Ventri-Cath™ 507; Millar Instruments, Houston, TX, USA) was inserted into the right carotid artery percutaneously and advanced into the LV under fluoroscopic guidance. The pressure–volume loops acquired from LV during six consecutive heart beats collected at end-expiratory apnea were recorded, and analyzes were recorded using the Millar Instruments MPVS Ultra™ system. The peak rate of LV pressure rise (dP/dt_{max}) and end-systolic elastance (E_{es}) was assessed as indices of contractility, and the time constant of isovolumic pressure decline (tau), peak rate of LV pressure decline (dP/dt_{min}), and maximal rate of early filling (dV/dt_{max}), as indices of lusitropy which were collected from first derivative of pressure curve of the LV. Left ventricular minimal early minimal pressure measured after mitral valve opening (P_{min}) and end-diastolic LV pressure (EDP) measured after atrial contraction were also evaluated.

2.5 | Systemic arterial pressure

Automated inflationary oscillometric blood pressure monitoring device BP-100D (Fukuda M.E., Tokyo, Japan) was used to assess systemic arterial pressure (SAP) in all dogs simultaneous with invasive hemodynamic measurements.

2.6 | Doppler echocardiography measurements

Echocardiography was performed using Aloka ProSound α7 (Hitachi Aloka Co., Tokyo, Japan) equipped with a 5-MHz transducer to obtain standard views in left lateral decubitus position. Left parasternal apical 4-chamber view was used to acquire mitral inflow: peak early diastolic filling (E wave), peak late diastolic filling velocities (A wave), E/A ratio, and velocity–time integral (VTI) measured from the Doppler time–velocity profiles; mitral annular early (E′) and late (A′) diastolic velocities, and septal mitral annular systolic velocity (Sm_S). E/E′ ratios were calculated from tissue Doppler signals of both sides of mitral valve annulus (E'_S: septal; E'_L: lateral wall). For each measurement, mean was collected from five cardiac cycles acquired during the period of brief apnea.

2.7 | Dobutamine infusion protocol

Incremental doses of dobutamine were administered to anesthetized dogs. Baseline hemodynamic and echocardiographic data were

TABLE 1 Hemodynamic effects of dobutamine administration in healthy (n = 6) and tachycardia-induced heart failure dogs (n = 6) under general anesthesia

	Infusion rate (μg kg^{-1} min^{-1})									
	0		2		4		8		12	
Variable	H	TIHF	H	TIHF	H	TIHF	H	TIHF	H	TIHF
Invasive hemodynamic measurements										
HR, beats/min	111 ± 20	102 ± 14	110 ± 25	106 ± 13	111 ± 30	116 ± 16	130 ± 30	128 ± 19	142 ± 31$^{*,\#,\$}$	142 ± 27$^{*,\#,\$}$
E_{es}, mmHg/ml	3.9 ± 1.8	1.7 ± 0.6†	4.3 ± 2.1	2.2 ± 1.1†	5.6 ± 2.9$^{*,\#}$	3.0 ± 1.3†	5.9 ± 3.1$^{*,\#}$	2.7 ± 0.8†	6.2 ± 5.1$^{*,\#}$	2.9 ± 1.4†
ESV, ml	31.1 ± 11.8	47.3 ± 9.2†	29.8 ± 10.27	42.5 ± 9.9	26.2 ± 9.4*	37.1 ± 10.4$^{*,\#}$	25.2 ± 9.5$^{*,\#}$	39.9 ± 8.2$^{*,\#}$	23.2 ± 8.4$^{*,\#}$	38.4 ± 9.8*,†
EDV, ml	47.0 ± 8.2	59.0 ± 7.7	46.9 ± 6.4	57.5 ± 10.3	46.0 ± 10.5	53.4 ± 13.7	40.3 ± 10.1*	49.6 ± 9.6$^{*,\#}$	36.8 ± 9.3$^{*,\#}$	49.0 ± 7.8*
ESP, mmHg	101.8 ± 11.0	74.0 ± 13.1	105.7 ± 9.9	81.8 ± 10.8	114.5 ± 5.1*	89.2 ± 14.8	117.2 ± 11.8*	95.7 ± 14.5*	119.0 ± 18.8*	96.9 ± 16.6*
EDP, mmHg	8.2 ± 2.7	11.5 ± 3.4	6.7 ± 3.1	12.2 ± 2.7	9.4 ± 4.7	13.6 ± 2.0†	11.3 ± 3.5	15.8 ± 3.2	9.4 ± 2.8	16.7 ± 5.9
dP/dt_{max}, mmHg/s	2,221 ± 571	1,115 ± 359†	2,783 ± 603	1,455 ± 589†	4,566 ± 841$^{*,\#}$	2,044 ± 761†	5,667 ± 1,209$^{*,\#}$	2,988 ± 1,324*,†	7,089 ± 1,499$^{*,\#,\$,+}$	3,808 ± 2,106$^{*,\#,\dagger}$
$-dP/dt_{min}$, mmHg/s	3,265 ± 471	1,864 ± 849†	3,803 ± 445	2,296 ± 863†	4,490 ± 970$^{*,\#}$	2,689 ± 1,072*,†	5,215 ± 1,207$^{*,\#}$	3,385 ± 1,122$^{*,\#,\dagger}$	4,918 ± 888$^{*,\#}$	3,558 ± 1,092$^{*,\#,\dagger}$
dV/dt_{max}, ml/s	159.8 ± 40.0	115.3 ± 23.1	193.3 ± 40.5	134.3 ± 26.8	226.3 ± 33.5*	144.8 ± 40.4†	252.5 ± 28.3$^{*,\#}$	154.5 ± 42.1*	279.0 ± 40.6$^{*,\#,\$}$	160.3 ± 48.3*,†
Tau, ms	28.2 ± 4.9	37.5 ± 11.4	25.6 ± 3.9	36.0 ± 9.6	24.0 ± 3.7*	32.6 ± 8.5*	20.2 ± 3.2$^{*,\#}$	29.3 ± 11.3$^{*,\#}$	17.1 ± 3.3$^{*,\#,\$}$	27.9 ± 12.3$^{*,\#,\$}$
Doppler echocardiography										
Peak E, cm/s	56.7 ± 11.2	36.5 ± 4.1†	58.1 ± 15.6	49.4 ± 11.8	67.0 ± 11.6*	61.1 ± 17.3*	78.4 ± 9.2$^{*,\#}$	70.2 ± 17.3*	82.4 ± 7.3$^{*,\#,\$}$	80.8 ± 23.0$^{*,\#,\$}$
EDT, ms	98.2 ± 41.5	101.3 ± 17.1	124.8 ± 42.2	105.8 ± 12.2	104.4 ± 28.1	111.8 ± 19.9	98.0 ± 20.2	106.3 ± 18.2	95.4 ± 24.6	97.9 ± 20.4
E/A ratio	1.37 ± 0.67	1.88 ± 0.92	1.38 ± 0.65	1.65 ± 1.11	1.42 ± 0.65	1.58 ± 0.51	1.38 ± 0.56	1.50 ± 0.55	1.28 ± 0.47	1.59 ± 0.60
Mitral VTI, cm	7.1 ± 1.7	5.4 ± 0.4	8.0 ± 0.9	6.9 ± 1.8*	9.2 ± 1.5*	8.3 ± 1.7*	9.4 ± 1.5*	9.6 ± 1.6$^{*,\#}$	9.5 ± 2.0*	9.9 ± 1.6$^{*,\#,\$}$
E/E'_S ratio	6.3 ± 1.8	8.9 ± 1.7†	5.8 ± 1.6	9.5 ± 2.2†	6.8 ± 1.0	9.1 ± 1.3†	7.0 ± 0.8	9.8 ± 1.2†	7.5 ± 0.9	10.3 ± 2.8†
E/E'_L ratio	7.3 ± 1.8	5.7 ± 1.6	6.3 ± 1.0	6.2 ± 1.6	6.4 ± 1.7	6.0 ± 1.1	6.5 ± 1.3	5.8 ± 1.6	6.6 ± 1.7	6.6 ± 1.5

Notes. Values in mean ± *SD*.

dP/dt_{max}: peak rate of ventricular pressure rise; dP/dt_{min}: peak rate of ventricular pressure decline; E′: early diastolic mitral annulus velocity (S, septal, L, lateral wall); EDP: end-diastolic pressure; EDT: early diastolic filling velocity deceleration time; EDV: end-diastolic volume; E_{es}: left ventricular end-systolic elastance; ESP: end-systolic pressure; ESV: end-systolic volume; HR: heart rate; peak A: late diastolic filling velocity; peak E: early diastolic filling velocity; P_{max}: peak systolic pressure; P_{min}: minimum early diastolic pressure; tau: time constant of isovolumetric relaxation; VTI: velocity–time integral.

$^{*}p < 0.05$ versus baseline of the same group; $^{\#}p < 0.05$ versus dobutamine 2 μg kg^{-1} min^{-1} of the same group; $^{\$}p < 0.05$ versus dobutamine 4 μg kg^{-1} min^{-1} of the same group; $^{+}p < 0.05$ versus dobutamine 8 μg kg^{-1} min^{-1} of the same group; $^{\dagger}p < 0.05$ versus healthy dogs at the same dose.

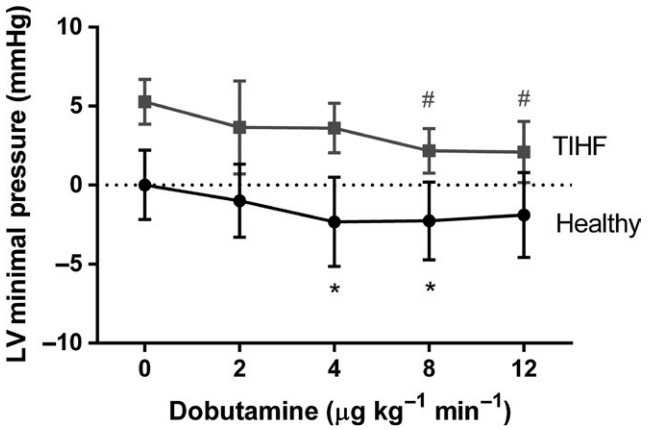

FIGURE 1 Mean ± *SD* values left ventricle minimal pressure (P_{min}) of healthy and tachycardia-induced heart failure dogs at baseline and during dobutamine titration. *$p < 0.05$ versus healthy group baseline; #$p < 0.05$ versus tachycardia-induced heart failure group baseline

recorded before start continuous infusion rate (CIR) of dobutamine and at the end of the infusion period. Dobutamine was infused intravenously over a period of 10 min with increasing titration at a rate of 2.0, 4.0, 8.0, and 12.0 μg kg^{-1} min^{-1} for same time periods.

2.8 | Statistical analysis

All results were reported as mean ± standard deviation (*SD*). Hemodynamic variables were analyzed and compared between healthy and after 8 weeks of RVAP at baseline. The same variables were collected from healthy and tachycardia-induced heart failure (TIHF) groups at each dose rate within the group. Lately, the effects of the each dose of dobutamine were compared between healthy and TIHF groups. All data sets were analyzed by repeated measure two-way ANOVA with Tukey or Sidak analysis for multiple comparisons and Holm-Sidak post-test for significant differences between healthy and TIHF groups. Linear regression with two-tailed paired t test was applied to determine correlation coefficients between hemodynamic variables, and Pearson's coefficient correlation determined the degree of association between hemodynamic and echocardiographic variables. *p*-values <0.05 were considered statistically significant. All statistical analyses were performed, and statistical images were generated using GraphPad Prism 6.0v (GraphPad Software Inc., San Diego, CA, USA).

3 | RESULTS

Mean ± *SD* values of hemodynamic measurements for healthy and TIHF dogs were assembled in the Table 1. Baseline measurements showed that contractility (dP/dt_{max}) and ventricular filling (dP/dt_{min}) were significantly reduced after 8 weeks of RVAP comparing with healthy group. RVAP resulted in increased ESV and reduced ESP comparing with healthy dogs. Although EDV was increased, the EDP was not greatly elevated as a result of LV enlargement without significant LV wall thickening.

In both healthy and TIHF groups, infusion of dobutamine at a dose of 2 μg kg^{-1} min^{-1} was associated with no significant changes in hemodynamic variables measured. In healthy dogs, dobutamine at a dose rate of 4 μg kg^{-1} min^{-1} or higher dose rates improved LV contractility, that is, increased E_{es} and dP/dt_{max}, LV relaxation (increased dP/dt_{min} and reduced tau), and ventricular filling (increased dV/dt_{max}) comparing with baseline measurements. In TIHF group, higher doses of dobutamine were required to improve contractility, relaxation, and LV filling. Dobutamine at a dose of 8 μg kg^{-1} min^{-1} or higher dose decreased EDV and improved LV performance in both groups.

An increasing trend in EDP of dogs of TIHF group was observed. EDP in TIHF group also tended to be higher in comparison with healthy dogs at each dose rate administered. Although LV contractility (dP/dt_{max}) and relaxation (dP/dt_{min}) indices have improved with administration of incremental dose rates of dobutamine in TIHF dogs, they were significantly lower than those measured in healthy dogs (healthy vs. TIHF group, $p < 0.05$ for each measurement at the same dose). Three healthy dogs presented negative LV minimal early diastolic pressure (P_{min} ranged from −0.57 to −12.7 mmHg). Only one of the six TIHF dogs presented negative minimal early diastolic pressure with lower P_{min} values at a dose rate of 8 μg kg^{-1} min^{-1} (Figure 1).

Analyses of relationship between methods showed that ESV was correlated with indices of isovolumic relaxation, dP/dt_{min} ($r = -0.47$, $p < 0.001$), tau ($r = 0.35$, $p < 0.01$), and minimal early diastolic pressure ($r = 0.37$, $p < 0.01$). Ejection fraction showed moderate correlation with tau (Figure 2) and strong correlation with dP/dt_{min} (Figure 3). Minimal early diastolic pressure (P_{min}) was positively correlated with tau ($r = 0.56$, $p < 0.0001$).

3.1 | Systemic arterial pressure

Both groups showed dose-related response to dobutamine infusion with significant elevation of SAP which were observed with higher doses in TIHF group (Figure 4).

3.2 | Doppler echocardiography

Variables collected from measurements of mitral annular systolic and diastolic velocities, and transmitral flow peak velocities are summarized in Table 1. Doppler mitral annular systolic velocities (Sm_S and Sm_L) augmented with dobutamine at a dose of 4 μg kg^{-1} min^{-1} in healthy dogs and at a dose of 8 μg kg^{-1} min^{-1} in TIHF dogs. At baseline, transmitral early peak E velocity and E/E'_S ratio were significantly elevated in TIHF group comparing with healthy group.

Mitral inflow VTI and septal mitral annular early diastolic velocity (E'_S) suggested dose-related improvement of LV filling and relaxation with infusion of dobutamine at a dose of 4 μg kg^{-1} min^{-1} or higher in both groups. Overall E/A ratio did not change significantly with incremental doses of dobutamine in healthy or TIHF group. However,

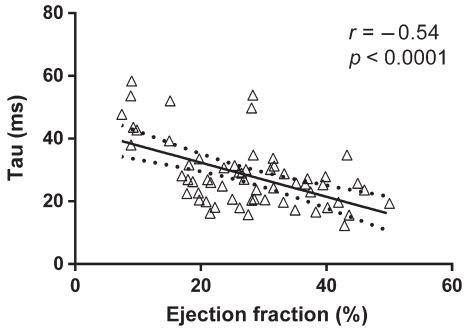

FIGURE 2 Tau and ejection fraction linear coupling. Data sets represent mean values of healthy and tachycardia-induced heart failure dogs at baseline and during dobutamine titration. The solid line represents linear regression ±95% confidence intervals (dashed lines)

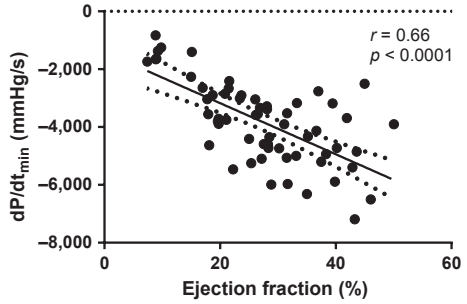

FIGURE 3 Peak rate of left ventricular pressure decline (dP/dt_{min}) and ejection fraction linear coupling. Data sets represent mean values of healthy and tachycardia-induced heart failure dogs at baseline and during dobutamine titration. The solid line represents linear regression ±95% confidence intervals (dashed lines)

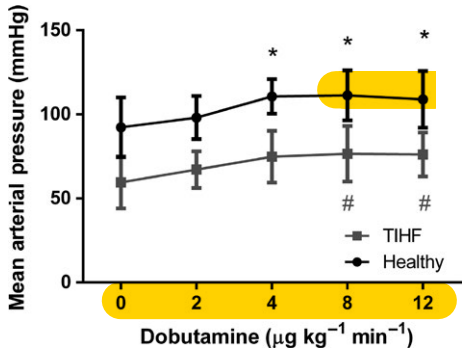

FIGURE 4 Peripheral arterial pressure measured using oscillometric method simultaneous to pressure–volume relationship measurements during dobutamine administration in healthy ($n = 6$) and tachycardia-induced heart failure dogs ($n = 6$) under general anesthesia

three dogs of TIHF presented high E/A ratio (restrictive flow pattern) at baseline and dose-related reduction of E/A ratio with significant improvement using dobutamine at a dose of 8 μg kg^{-1} min^{-1} (1.66 ± 0.40 vs. 2.83 ± 0.45, $p < 0.05$ vs. baseline E/A ratio, $n = 3$).

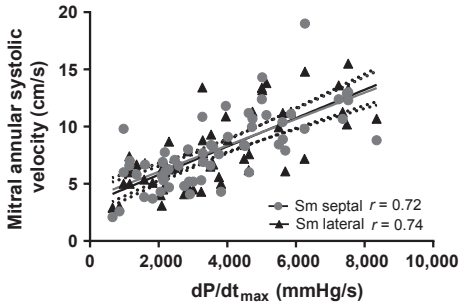

FIGURE 5 Peak rate of left ventricular pressure rise (dP/dt_{max}) and Doppler-derived longitudinal mitral annular systolic velocity relation. Data sets represent mean values of healthy and tachycardia-induced heart failure dogs at baseline and during dobutamine titration. The solid line represents linear regression, gray circles from septal site, and black triangles from lateral free wall site, ±95% confidence intervals (dashed lines). Both $p < 0.0001$

3.3 | Correlation between variables measured through echocardiography and catheterization

Analyses of PV relation and Doppler echocardiography-derived variables showed strong correlation between dP/dt_{max} (index of contractility) and mitral systolic velocities at septum and lateral wall at baseline and after TIHF (Figure 5). Analyses of indices of relaxation (tau and dP/dt_{min}) in both groups showed a weak negative correlation only between tau and E/E'_S ratio at baseline and during dobutamine infusion (Figure 6). Septal mitral annular early diastolic velocity (E'_S) showed inverse correlation with the P_{min} ($r = -0.44$, $p < 0.001$) and dP/dt_{min} ($r = -0.52$, $p < 0.001$).

4 | DISCUSSION

4.1 | Effects of chronic RVAP

Chronic RVAP results in progressive LV dilatation and asymmetric wall thinning which reduce diastolic untwist, prolong relaxation, and consequently increase diastolic filling pressure (Fukuta & Little, 2008; Prinzen & Peschar 2002). Structural and electrical remodeling and their effects on LV function as consequence of RVAP have been studied in humans (Gillis, 2006; Prinzen et al., 1995). However, the development of heart failure associate with pacemaker lead implantation at the apex and the importance of cardiac dysfunction after long-term pacing in dogs remain unclear (Nakata et al., 2016).

4.2 | Dobutamine effects in healthy group

In healthy subjects, during increased chronotropic and inotropic states, cardiac output, pulmonary venous, and systemic arterial pressures are maintained at normal range by reducing the minimal early diastolic pressure and increasing AVPG which consequently enhance early LV filling (Eichhorn et al., 1992; Remme et al., 2011; Udelson et al., 1990). Nonetheless, significant diastolic dysfunction might be present only during exercise despite normal filling pressures at rest.

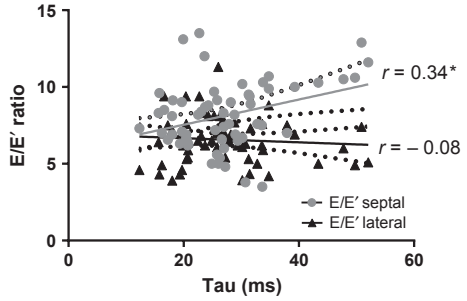

FIGURE 6 Septal and lateral wall E/E′ ratio and time constant of pressure decline relation. Data sets represent mean values of healthy and tachycardia-induced heart failure dogs at baseline and during dobutamine titration. The solid line represents linear regression, gray circles from septal site, and black triangles from lateral free wall site, ±95% confidence intervals (dashed lines). *$p < 0.05$

In the present study, administration of incremental dose rates of dobutamine produced a gradual reduction of minimal early diastolic pressure and more rapid isovolumic relaxation in healthy dogs. In addition, administration of dobutamine at 4 μg kg^{-1} min^{-1} provided significant improvement in contractility (E_{es} and dP/dt_{max}), relaxation (dP/dt_{min} and tau), and LV filling (dV/dt_{max}) comparing with baseline data.

Peripheral sympathetic inhibitory activity on the heart during dobutamine administration results in reduction of HR along with elevation in SAP (Velez-Roa, Renard, Degaute, & Van de Borne, 2003). Dobutamine is administered in racemic mixture, and peripheral vascular effects of α1-mediated vasoconstriction may be compensated by β2-mediated vasodilatation (Westfall & Westfall, 2006). Our results showed that dobutamine at a dose of 4 μg kg^{-1} min^{-1} or higher dose increases cardiac output accompanied by increases in SAP in healthy dogs, while the same effect has been observed in humans at a dose of 3 μg kg^{-1} min^{-1} (Velez-Roa et al., 2003). Heterogenous hemodynamic effects of dobutamine have been investigated in experimental and clinical settings and might differ greatly even between healthy subjects (Dubin, Lattanzio, & Gatti, 2017).

4.3 | Dobutamine effects in TIHF group

After 8 weeks of RVAP, LV dilatation (increased ESV and EDV) associated with reduced peak rate of LV pressure rise and peak rate of LV pressure decline suggested presence of contractility depression and altered relaxation. The mechanism involved in LV dysfunction might be related to reduced cAMP and end-diastolic calcium levels in failing hearts (Morgan, Erny, Allen, Grossman, & Gwathmey, 1990). Additionally, dyssynchrony or abnormal segmental contractions caused by RVAP may increase the nonuniform distribution of load and nonuniform inactivation in space and time which are responsible for abnormal relaxation (Blaustein & Gaasch, 1983; Brutsaert, Rademakers, & Sys, 1984; Ghosh & Kovacs, 2012). Udelson, Cannon, Bacharach, Rumble, and Bonow (1989) suggested that isoproterenol administration, a β-AR agonist, may temporally improve LV early filling synchrony in humans with hypertrophic cardiomyopathy even in the presence of ischemia. However, the administration of high doses of β-AR agonists were related to short- and long-term detrimental adverse effects including elevation of atrial pressure due to increased venous return, elevation of pulmonary artery pressure, myocardial ischemia, and increased risk of arrhythmias in patients with HF (Binkley, Murray, Watson, Myerowitz, & Leier, 1991; Faggiano et al., 1998; Francis, Bartos, & Adatya, 2014; Tatsumi et al., 2010). The present study suggested that LV filling can be improved in subjects with RVAP through dobutamine stimulation with generation of lower early diastolic pressures, even though the minimal early diastolic pressures do not reach negative values; however, higher doses (12 μg kg^{-1} min^{-1}) might have detrimental effects on LV filling due to incomplete relaxation (combination of prolonged isovolumic relaxation time and increased heart rate). Previous studies showed that the cAMP produced by dobutamine stimulation may be better compartmentalized for the elevation of local cAMP for lusitropic response (faster relaxation) than for inotropic response in failing hearts (Tanigawa et al., 2000). Consequently, while contractile reserve might be significantly reduced, the lusitropic response to dobutamine might be preserved though diminished. In fact, the infusion rate of dobutamine required to improve contractility (8 μg kg^{-1} min^{-1} or higher dose) after 8 weeks of RVAP was higher than that required to improve LV relaxation (4 μg kg^{-1} min^{-1}) comparing with baseline values. A possible explanation for higher overall dobutamine dose required for improvement of LV function may be related to alterations in β-AR sensitivity, density, and function or alteration of contractile response to catecholamines with aging and contractility-dependent enhancement of lusitropy (Long & Kirby, 2008; Velez-Roa et al., 2003). In fact, relaxation may also deteriorate rapidly along with the reduction of systolic function which can be partially reversed through the administration of β-AR agonists (Chuang, Triposkiadis, & Starling, 2008; Katz, 1988). Accordingly, ejection fraction showed significant correlation with relaxation indices along with administration of incremental doses of dobutamine. The degree of LV contraction below its equilibrium volume and the release of energy stored during contraction, that is, elastic restoring forces, during administration of a β-AR agonist were previously studied and showed to be proportional to the extent of elastic recoil with generation of rapid LV pressure fall (increased dP/dt_{min} and reduced tau) and lower minimal early diastolic pressures (Udelson et al., 1990). Nevertheless, energy storage is diminished in hearts with systolic dysfunction and the energy released during diastole is likewise affected which may result in reduced elastic recoil, prolonged relaxation, and decreased suction effect or increased P_{min} (Firstenberg et al., 2001).

Dobutamine at a dose of 12 μg kg^{-1} min^{-1} induced larger increases in SAP and might have reduced arterial baroreflex sensitivity (Van de Borne et al., 1999). In this case, increases in cardiac output are based on increases in HR. In contrast, the hemodynamic effects of lower doses of dobutamine, improving inotropy and lusitropy without significant changes in blood pressure, might result from antagonism of individual isomers (Al-Hesayen, Azevedo, Newton, & Parker, 2002; Parker et al., 1991; Ruffolo & Yaden, 1983).

4.4 | Echocardiography

Doppler echocardiographic variables provide a noninvasive method for assessment LV relaxation and longitudinal contraction (Parker et al., 1991; Yotti et al., 2005). The peak rate of LV pressure decline may influence the mitral annular early diastolic velocity which suggested that E'_S might estimate early relaxation state. However, E′ is modified by end-diastolic pressure, hence, it might have influenced E/E'_S ratio. LV lengthening changes observed only at the septal mitral annulus after 8 weeks of RVAP suggested early signal injury as previously described in a study showing abnormal segmental contraction localized at septal (vs. lateral) region and its predictive value for therapeutic response (Henn et al., 2015).

Transmitral flow velocities and flow patterns reflect LV relaxation (Flachskampt et al., 2015). In failing hearts with diastolic dysfunction, the relaxation time is prolonged, the peak rate of LV pressure decline (dP/dt_{min}) is decreased, and minimal early diastolic pressure (P_{min}) increases reflecting a lower AVPG. Therefore, the early mitral inflow velocity (E) diminishes along with increases in deceleration time and the peak late velocity (A) tends to increase in attempt to overcome elevated LV pressures (Flachskampt et al., 2016). Nonetheless, transmitral flow Doppler-derived variables are preload-dependent and might also present pseudonormal pattern (unchanged E/A ratio) under dobutamine stimulation in hearts with concomitant systolic dysfunction (Chuang et al., 2008; Yamamoto et al., 1993). In addition, greater negative effect on relaxation might be expected when end-systolic elastance further decreases to values below that collected at 8 weeks of RVAP (Eichhorn et al., 1992). In this condition, late ventricular filling may compensate the reduction of early LV filling and alter Doppler filling pattern (low E/A ratio) though it still might not reflect augmented atrial pressure resultant from systolic dysfunction (Yamamoto et al., 1993).

4.5 | Limitations of the study

Limitations of the study that may have influenced the results include the small sample size. Although the pacemaker stimulation rate used in this study differs from the chronic RVAP with electric stimulation at lower frequencies used for the treatment of rhythm disorders, both conditions may result in heart failure associate with altered LV filling and myocardial dysfunction. In addition, dobutamine may accumulate and some dogs may present a late peak of effects, therefore, in a clinical setting prolongation, dobutamine infusion period might be required until the maximal effect is observed (Weissman, Nidorf, Guerrero, Weyman, & Picard, 1995). Nonetheless, administration of a β-AR agonist for long periods impairs β-AR function and therapy effectiveness may be limited by cAMP levels in the failing myocardium.

5 | CONCLUSIONS

Left ventricle filling conditions and pulmonary hemodynamics might be improved through the augment of AVPG for a given left atrial pressure (within the physiological range), reduction of minimal early diastolic pressure, and faster relaxation which may be achieved through dobutamine titration (4–8 μg kg^{-1} min^{-1}). Nonetheless, atrial pressure elevation associated with systolic dysfunction and LV remodeling may adversely affect ventricular filling. The present results suggested that long-term RVAP results in attenuation of lusitropic response and significant reduction of inotropic response to dobutamine administration with relatively preserved contraction–relaxation coupling. Though dobutamine infusion resulted in dose-related limited improvements in LV filling, the deleterious effects on diastolic function at high dose-rate ranges in dogs with RVAP-induced cardiac dysfunction should be considered for therapeutic decision during an anesthetic procedure.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests with respect to the research, authorship, and/or publication of this article.

AUTHORS' CONTRIBUTIONS

All authors have read and approved the final manuscript. T.M. Nakata gave substantial contributions to conception, data analysis, and interpretation of data; drafting the manuscript; gave final approval of the version to be published; agreed to be accountable for all aspects of the work in insuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. H. Kaji gave substantial contributions to design, data analysis, and interpretation of data; revised the manuscript critically for important intellectual content; gave final approval of the version to be published; agreed to be accountable for all aspects of the work in insuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. N. Matsuura gave substantial contributions to acquisition of data, data analysis, and interpretation of data; revised the manuscript critically for important intellectual content; gave final approval of the version to be published; agreed to be accountable for all aspects of the work in insuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. M. Shimizu gave substantial contributions to conception and design, data analysis, and interpretation of data; revised the manuscript critically for important intellectual content; gave final approval of the version to be published; agreed to be accountable for all aspects of the work in insuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. R. Tanaka gave substantial contributions to conception and design, data analysis, and interpretation of data; drafting the manuscript;

gave final approval of the version to be published; agreed to be accountable for all aspects of the work in insuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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