ORIGINAL ARTICLE

Noninvasive assessment of intraventricular pressure difference in left ventricular dyssynchrony using vector flow mapping

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Abstract

Diastolic intraventricular pressure difference (IVPD) reflects left ventricular (LV) diastolic function. The relative pressure imaging (RPI) enables the noninvasive quantification of IVPD based on vector flow mapping (VFM) and visualization of regional pressure distribution. LV dyssynchrony causes deterioration of cardiac performance. However, it remains unclear how IVPD is modulated by LV dyssynchrony. LV dyssynchrony was created in ten open-chest dogs by right ventricular (RV) pacing. The other ten dogs undergoing right atrial (RA) pacing set at the similar heart rate with RV pacing were used as controls. Echocardiographic images were acquired at baseline and during pacing simultaneously with LV pressure measurement by a micromanometer. Pressure difference (ΔP) was computed between the apex and the base of the LV inflow tract during a cardiac cycle by RPI and ΔP during isovolumic relaxation time (ΔP_{IRT}), a parameter of diastolic suction, and that during early filling phase (ΔP_E) were measured. During RV pacing, stroke volume (SV) and ΔP_{IRT} decreased significantly, while ΔP_E did not change compared to the baseline. During RA pacing, SV, ΔP_{IRT} and ΔP_E did not change significantly. ΔP_{IRT} tended to correlate with $-dP/dt_{min}$ and end-systolic volume, and significantly correlated with ejection fraction. IVPD during isovolumic relaxation time was decreased by LV dyssynchrony, while IVPD during early filling phase was not. A reduction of diastolic suction is observed in LV dyssynchrony and is significantly related to a decrease in SV.

Keywords Vector flow mapping · Diastolic function · Intraventricular pressure difference · Left ventricular dyssynchrony

Introduction

Intraventricular pressure difference (IVPD) exists in the left ventricle (LV) through a cardiac cycle and it has been shown to be associated with cardiac function [1–3]. IVPD during early diastole has been reported to reflect LV diastolic suction as well as diastolic filling [4–6]. Since suction plays an important role in promoting early rapid filling and accepting adequate filling volume under low filling pressure, IVPD may be an additional marker to assess diastolic suction and diagnose diastolic dysfunction. As a noninvasive method of evaluating IVPD, color M-mode Doppler

(CMMD) echocardiography integrating the Euler equation has been proposed [7]. However, this method is applied only to a single direction, parallel to the beam path.

Vector flow mapping (VFM®, Hitachi) is a new echocardiographic technology to evaluate intracardiac flow velocity vectors. It can assess flow velocity in the direction not only parallel but also perpendicular to the beam based on the combination of the continuity equation and speckle tracking echocardiography [8]. The velocity information can be converted to the pressure information using the Navier–Stokes equation (NSE) and noninvasive assessment of intraventricular two-dimensional distribution of relative pressures is now feasible with a software developed by Hitachi (Relative Pressure Imaging (RPI), Hitachi Co.) [9].

Some patients with heart failure have LV dyssynchrony accompanying electrical conduction abnormalities such as left bundle branch block (LBBB) [10]. Inefficient LV work due to dyssynchronous wall motion causes deterioration of cardiac performance and results in the adverse prognosis [11]. Dyssynchronous LV contraction affects the following

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relaxation [10]. However, it remains unclear how diastolic IVPD is modulated by LV dyssynchrony.

In the present study, we analyzed IVPD noninvasively using RPI before and during LV dyssynchrony induced by right ventricular (RV) pacing and investigated the mechanism of impaired diastolic function in LV dyssynchrony.

Methods

Animal preparation

Our experimental study was approved and conducted in accordance with the rules of the animal experiments committee of Osaka University. Twenty open-chest dogs (female, 9.9 ± 0.7 kg) were used in this study. After intramuscular injection of xylazine hydrochloride (0.5 mg/kg), the dogs were anaesthetized by pentobarbital sodium (25.9 mg/kg) administered via a peripheral vein and then were intubated and ventilated with room air and oxygen using a Harvard respirator (SN-480–3, Shinano, Tokyo, Japan). Oxygen saturation and electrocardiogram were continuously monitored. After induction of anesthesia, the dogs were placed in supine position, and continuous intravenous infusion of lactated Ringer's solution was administered via a peripheral vein. Anesthesia was maintained through continuous infusion of pentobarbital sodium (6 mg/kg/h) and midazolam (0.18 mg/kg/h). Buprenorphine (4 µg/kg) was administered intramuscularly for analgesia. Pancuronium bromide (1.0 mg) was administered intravenously as a muscle relaxant. The chest was opened through a thoracotomy in the longitudinal direction and the heart was suspended in a pericardial cradle.

A 6-Fr micromanometer catheter (Millar Instruments, Houston, Texas) was inserted into the LV through the right femoral artery or right common carotid artery to measure pressure. LV systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), maximum and minimum time derivatives of LV pressure (dP/dt$_{max}$, dP/dt$_{min}$) and time constant of LV relaxation (tau) were averaged for five consecutive beats. Tau was calculated assuming non-zero asymptote in the data from the point of the minimum time derivatives of the LV pressure to the point at which pressure decreased to the level of the LVEDP.

Echocardiography

The ultrasound equipment was Prosound F75 (Hitachi, Ltd., Tokyo, Japan). Apical long-axis color Doppler images were obtained using a UST-52124 probe, at a transducer frequency of 5 MHz, depth of 7 cm, and frame rate of 35–46 frames/second. The timings of aortic valve closure (AVC) and mitral valve opening (MVO) were determined from LV outflow tract (LVOT) flow and transmitral flow images obtained using pulsed wave Doppler echocardiography. Stroke volume (SV) was calculated using velocity–time integral of LVOT flow and LVOT diameter. Ejection fraction (EF) was calculated at the apical four-chamber view by the simplified Simpson's formula. Echocardiographic images were captured over five successive beats and echocardiographic parameters were averaged for three successive beats.

Experimental protocol

LV dyssynchrony was induced by RV pacing in ten dogs using a 4F pacing catheter connected to the external pulse generator (Canute, Welwyn Garden, UK). This pacing catheter was inserted into the RV from the right femoral vein, using echocardiographic imaging as a guide. We confirmed the creation of LV dyssynchrony by prolonged QRS duration by the electrocardiogram and dyssynchronous wall motion by two-dimensional echocardiography. We also measured time difference (TD) between the first peaks of longitudinal strain at the apical anterior and mid inferolateral segments. As a control with heart rate similar to RV pacing, right atrial (RA) pacing was performed in the other ten dogs using the electrode attached to the RA appendage. Each pacing rate was set at about 150 ppm (151 ± 2 ppm) and a stable condition was ensured. Echocardiographic images, heart rate and LV pressure were acquired at baseline and during each pacing.
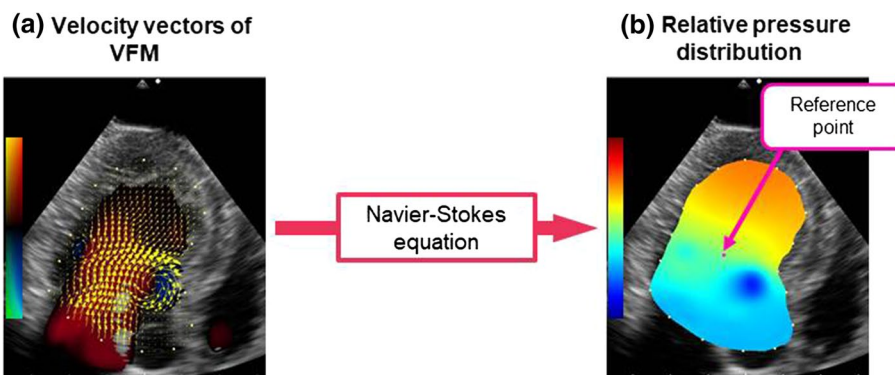
Image analysis

RPI, a new noninvasive method to calculate intracardiac pressure distribution, uses velocity field of VFM and the momentum equation. Intraventricular flow velocity vectors of VFM are computed by solving the continuity equation using flow velocity obtained from color Doppler and wall velocity obtained from speckle tracking echocardiography [12, 13]. RPI method converts this velocity information to relative pressure distribution using the momentum equation of fluid motion named NSE (1) (Fig. 1).

$$\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = -\frac{1}{\rho}\frac{\partial p}{\partial x_i} + v\left(\frac{\partial^2 u_i}{\partial x_i \partial x_j}\right) \tag{1}$$

We use two-dimensional NSE by omitting terms related to the third direction because velocity field of VFM is two dimensional. To reduce the size of the system of equations, the divergence operation is applied to the NSE [9]. Pressure distribution is visualized by describing higher pressure as warm color and lower pressure as cold color relative to a reference point. The reference point has a pressure value of 0 mmHg and is automatically set at the center of the region of interest.

Fig. 1 Relative pressure imaging. Velocity information of VFM can be converted to pressure information based on the Navier–Stokes equation. **a** Yellow arrows represent regional flow velocity vectors of VFM. **b** The color map reflects relative pressure distribution. Warm color indicates higher and cold color indicates lower pressure relative to reference point that is automatically set at the center of the region of interest

In this study, color Doppler apical long-axis images were analyzed offline by using VFM analysis software (DAS-RS 1, Hitachi, Ltd.). The endocardial border was manually traced at end-diastole and then automatically determined throughout the remaining frames. The wall velocity was determined by speckle tracking echocardiography and then intraventricular pressure distribution was visualized. By setting a sampling line in the region of interest, a pressure difference between both ends of the line is calculated automatically. The pressure difference between the apex and the base of the LV inflow tract (ΔP) was computed during a cardiac cycle and peak ΔP during isovolumic relaxation time (ΔP_{IRT}) and that during early filling phase (ΔP_E) were measured (Fig. 2). These IVPD parameters were averaged for three consecutive cardiac cycles.

Statistical analysis

All values were shown as mean $\pm$ SD. Baseline and pacing conditions were statistically compared using paired t tests. RV pacing and RA pacing conditions were statistically compared using unpaired t tests. The Pearson product–moment

correlation coefficient was used to identify relationships between selected variables. Significance level was set at $P < 0.05$.

Results

Hemodynamics and echocardiographic data

Hemodynamics and echocardiographic data at baseline and during pacing are shown in (Table 1). Heart rate increased and LVEDP decreased significantly by RV and RA pacing. LVSP, dP/dt$_{max}$, dP/dt$_{min}$, SV and EF significantly decreased by RV pacing. Prolongation of TD was consistent with successful creation of LV dyssynchrony with RV pacing.

Relative pressure imaging

Figure 3 shows representative ΔP profiles at baseline and during each pacing and (Table 2) shows changes in ΔP_{IRT} and ΔP_E. During RV pacing, ΔP_{IRT} decreased significantly,
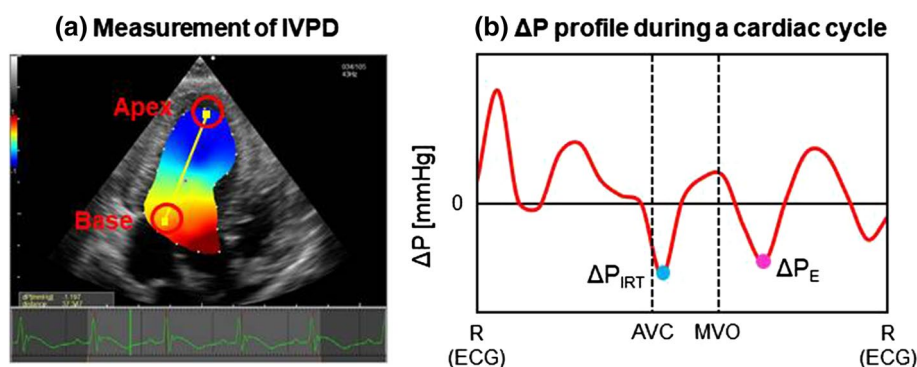
Fig. 2 Measurement of IVPD. **a** By setting a sampling line (*yellow line*) in the region of interest, a pressure difference between both ends of the line is calculated automatically. In the present study, pressure difference (ΔP) was computed between the apex and the base of the LV inflow tract frame by frame during a cardiac cycle. **b** ΔP profile

during one cardiac cycle. The negative value means the apical pressure is lower than the basal pressure. ΔP during isovolumic relaxation time (ΔP_{IRT}) and that during early filling phase (ΔP_E) were measured. *AVC* aortic valve closure; *MVO* mitral valve opening

Table 1 Hemodynamics and echocardiographic data

	RV pacing ($n = 10$)		RA pacing ($n = 10$)	
	Baseline	Pacing	Baseline	Pacing
Heart rate (bpm)	120 ± 14	145 ± 7*	122 ± 11	149 ± 6*
TD (ms)	40.3 ± 25.9	187.3 ± 42.9*	49.7 ± 42.9	43.7 ± 33.2
LVSP (mmHg)	106 ± 13	93 ± 11*†	113 ± 21	113 ± 22
LVEDP (mmHg)	4.5 ± 1.1	3.4 ± 1.2*	4.6 ± 2.3	2.5 ± 1.7*
dP/dt$_{max}$ (mmHg/s)	2294 ± 497	1880 ± 317*†	2588 ± 566	2750 ± 613
dP/dt$_{min}$ (mmHg/s)	-2112 ± 397	-1525 ± 341*†	-2158 ± 429	-2191 ± 626
Tau (ms)	43.0 ± 5.7	48.7 ± 13.8	41.3 ± 6.4	41.9 ± 5.1
SV (ml)	13.3 ± 3.3	10.4 ± 3.5*	15.6 ± 3.9	13.7 ± 2.6
EF (%)	67.7 ± 11.2	58.2 ± 10.6*	67.9 ± 10.6	65.7 ± 8.2

TD time difference between first peaks of longitudinal strain at the apical anterior and mid inferolateral segments; *dP/dt$_{max}$* maximum time derivative of left ventricular pressure; *dP/dt$_{min}$* minimum time derivative of left ventricular pressure; *EF* left ventricular ejection fraction; *LVEDP* left ventricular end-diastolic pressure; *LVSP* left ventricular systolic pressure; *SV* stroke volume

*$P < 0.05$ vs. baseline, †$P < 0.05$ vs. RA pacing
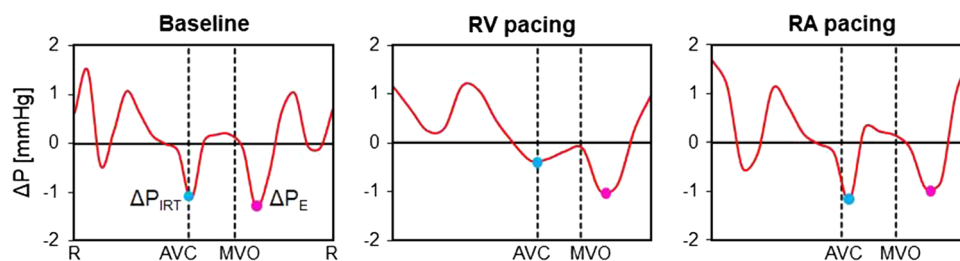
Fig. 3 Representative ΔP profiles at baseline and during each pacing. The Y axis indicates pressure difference (ΔP) between the apex and the base of the inflow tract, and the X axis indicates R–R interval. During RV pacing, ΔP$_{IRT}$ decreased while ΔP$_E$ did not change. During RA pacing, ΔP$_{IRT}$ and ΔP$_E$ did not change. *AVC* aortic valve closure; *MVO* mitral valve opening

Table 2 IVPD parameters

	RV pacing ($n = 10$)		RA pacing ($n = 10$)	
	Baseline	Pacing	Baseline	Pacing
ΔP$_{IRT}$ (mmHg)	-0.72 ± 0.29	-0.39 ± 0.18 *	-0.62 ± 0.31	-0.66 ± 0.35
ΔP$_E$ (mmHg)	-1.08 ± 0.29	-0.96 ± 0.39	-1.13 ± 0.44	-1.31 ± 0.63

ΔP$_{IRT}$ pressure difference during isovolumic relaxation time; *ΔP$_E$* pressure difference during early filling phase

*$P < 0.05$ vs. baseline

while ΔP$_E$ did not change compared to the baseline. During RA pacing, ΔP$_{IRT}$ and ΔP$_E$ did not change significantly. Representative relative pressure images during a cardiac cycle are shown in (Fig. 4). Relative pressure images during isovolumic relaxation time showed IVPD during RV pacing was lower than that at baseline and during RA pacing. Interestingly, in 8 out of 10 dogs during RV pacing, accompanying early septal contraction, a significant pressure gradient between the posterior area and the septal area (warmer color in the septal area indicating posterior pressure < septal pressure) was detected at early systole, while in all dogs at baseline and during RA pacing the significant horizontal pressure gradient was not detected at early systole.

Correlation between ΔP$_{IRT}$ and systolic or diastolic parameters

ΔP$_{IRT}$ correlated significantly with EF ($r = -0.52$, $P = 0.02$). Furthermore, ΔP$_{IRT}$ tended to correlate with dp/dt$_{min}$ ($r = 0.40$, $P = 0.09$) and tau ($r = 0.42$, $P = 0.11$), although these did not reach statistical significance. ΔP$_{IRT}$ did not correlate with dP/dt$_{max}$ (Fig. 5).

Fig. 4 Representative relative pressure images during a cardiac cycle. Warm color indicates higher and cold color indicates lower pressure relative to the reference point. Images during isovolumic relaxation time showed lower IVPD during RV pacing compared with baseline and RA pacing. The pressure gradient from the posterior to the septal side (warmer color at the septal side) accompanying early septal contraction existed during RV pacing. *AVC* aortic valve closure; *MVO* mitral valve opening
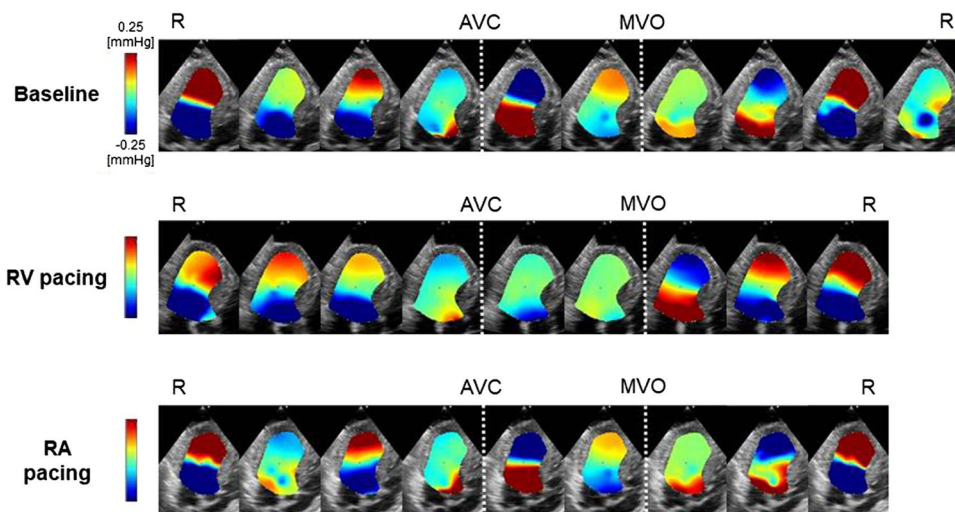
Fig. 5 Relationships between ΔP_{IRT} and systolic and diastolic parameters. The black circles indicate the data obtained during RV pacing and the white circles indicate the data obtained during RA pacing. A significant correlation was found between ΔP_{IRT} and EF. dP/dt_{max} maximum time derivative of left ventricular pressure; dP/dt_{min} minimum time derivative of left ventricular pressure; EF, LV ejection fraction; tau, time constant of LV relaxation
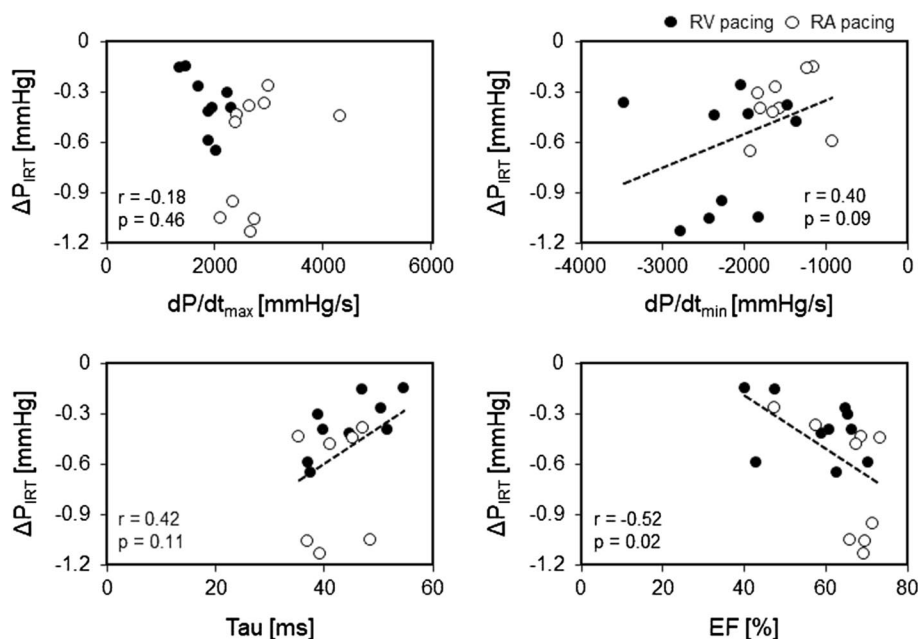
Discussion

In the present study, we investigated how IVPD was changed by LV dyssynchrony using VFM. IVPD during isovolumic relaxation time was decreased by LV dyssynchrony induced by RV pacing. In contrast, in RA pacing it was not changed. IVPD during isovolumic relaxation time was associated with EF.

Measurement of IVPD

Noninvasive estimation of IVPD based on CMMD echocardiography is a well-validated technique [1, 5, 14].

However, this method can assess only pressure difference along a straight scan line. RPI is a novel method based on velocity vectors obtained by VFM and the NSE [9]. In addition to measurement of a pressure difference, it allows visualization of intraventricular pressure distribution. Thus, RPI may reveal how pressure distribution is modulated by various heart diseases. In the present study, the decrease in intraventricular pressure gradient during isovolumic relaxation time in LV dyssynchrony was detected visually as shown in (Fig. 4). In addition, the pressure gradient from the posterior to the septal side was observed accompanying dyssynchronous early septal contraction. It is considered that remarkable pressure gradient in the horizontal direction would not be generated if all LV segments contract in a synchronous manner. Therefore,

the posterior to septal pressure gradient may be caused by dyssynchronous wall motion.

Previous studies have focused on IVPD during early filling phase mainly [5, 7]. However, we focused on IVPD during not only early filling phase but also isovolumic relaxation time. During isovolumic relaxation time, although both the aortic valve and mitral valve are closed, apically directed flow have been detected in the intact LV with CMMD and pulsed wave Doppler echocardiography [15, 16]. That proves pressure difference between LV apex and base exists during isovolumic relaxation and this IVPD is considered as the force to redistribute the blood in the LV and promote early diastolic filling [15]. We considered IVPD during isovolumic relaxation time should reflect LV suction and provide valuable insight into LV diastolic and systolic function. Yotti et al. defined peak IVPD that was reached during isovolumic relaxation time, just after AVC as reverse ejection IVPD. They showed reverse ejection IVPD reflected the rate of LV relaxation.[1] Furthermore, Nagomi et al. showed that kinetic energy of isovolumic relaxation flow calculated by VFM associated with systolic function, LV geometry and untwisting mechanics [6].

IVPD in LV dyssynchrony

RV pacing induces an abnormal activation sequence and dyssynchronous ventricular contraction comparable with LBBB. Subsequently, dyssynchronous LV relaxation also occurs. A previous study demonstrated dyssynchronous strain curve in diastole in patients with LBBB and with RV pacing [10]. Using CMMD echocardiography, Lin et al. observed that apically directed flow during isovolumic relaxation time was disturbed by RV apical pacing. They considered that it reflected the disruption of intraventricular pressure gradient during isovolumic relaxation time [16]. In the present study, IVPD during isovolumic relaxation time was decreased by LV dyssynchrony. This showed apical LV pressure was hard to decrease during isovolumic relaxation time due to abnormal LV relaxation following dyssynchronous contraction.

LV suction relates closely with systolic function because the elastic recoil plays an important role in generating LV sucking effect [17]. When the LV contracts below its equilibrium volume, the potential energy is stored during systole. Due to release of potential energy during early diastole, LV relaxation is promoted [18]. Yanada et al. indicated that velocity of apically directed isovolumic relaxation flow correlated with EF and early diastolic propagation velocity, and concluded isovolumic relaxation flow played a role in delivering good LV systolic performance to LV early diastolic filling [15]. Nakatani et al. showed the peak negative LV pressure during mitral occlusion which was measured as an index of suction strongly

and negatively correlated with EF and tended to correlate with dP/dt$_{min}$ in the human ventricle [17]. In the present study, IVPD during isovolumic relaxation time correlated with EF moderately and negatively, and tended to correlate with dP/dt$_{min}$ and tau comparable with those previous studies. In addition to dyssynchronous LV relaxation, reduction of elastic recoil due to systolic dysfunction may also induce reduction of IVPD during isovolumic relaxation time leading to a decrease in SV.

Clinical perspective

Heart failure patients with LV dyssynchrony can be treated by cardiac resynchronization therapy (CRT). Recently, intracardiac flow dynamics have been studied in heart failure patients with implanted CRT. Goliasch et al. reported that the timing of the onset of the diastolic vortex from mitral valve opening was delayed during deactivation of CRT and it was recovered instantly by reactivation [19]. Also, Pedrizzeti et al. found that the orientation of blood flow momentum was changed by active CRT in good responders [20]. In the present study, we found changes in intraventricular pressure difference in LV dyssynchrony. Because the present study was still in the experimental stage, further studies are needed to examine whether intraventricular pressure characteristics can be an additional marker of response to CRT in clinical settings.

Limitations

Dog's heart rate was high especially during pacing, which hinders precise evaluation of IVPD during early and late filling phase. Also, this limitation may cause underestimation of true IVPD. Tanaka et al. compared IVPD obtained by RPI with two pressure sensors using a LV phantom to validate the RPI method. They reported that peak diastolic IVPD by RPI was underestimated by about 35% mainly because of insufficient frame rate of color Doppler echocardiography [9]. We compared IVPDs between RA pacing and RV pacing at the similar heart rate. Therefore, the effect of underestimation may be minimized. We used different dogs for RV pacing and RA pacing because we wanted to avoid a possible cardiac damage from a pacing protocol and the other running experimental protocol. Intraventricular pressure gradient has three-dimensional distribution. However, VFM is not applied to three-dimensional echocardiography at present. The existence of through-plane flows may contribute partly to underestimation of IVPD. To improve the accuracy of IVPD measurement using RPI, three-dimensional VFM is needed.

Conclusion

RPI based on VFM showed changes of intraventricular pressure distribution and difference in LV dyssynchrony induced by RV pacing. IVPD during isovolumic relaxation time was decreased by LV dyssynchrony. Decrease in IVPD during isovolumic relaxation time may reflect reduction of suction and decrease stroke volume.

Compliance with ethical standards

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