Effects of Volume Loading on Pulmonary Venous Flow and its Relation to Left Atrial Functions

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Although pulmonary venous (PV) flow is closely related to left atrial (LA) pressure dynamics, few investigators have discussed it in relation to LA functions, ie, reservoir, conduit, and booster pump functions. We examined changes in PV flow rate, LA dimension, and left ventricular filling volume in 11 dogs, and assessed the effects of multistaged volume loading on PV flow and LA functions. Systolic PV flow rate (S) increased significantly and reached a plateau, reflecting a limited LA reservoir function. Diastolic PV flow rate (D) increased significantly with an increase in LA pressure. S/D ratio increased non-significantly from 0.87 ± 0.07 before volume loading to 0.96 ± 0.08 until S reached a plateau and then decreased to 0.76 ± 0.08 ($p < 0.05$) because of a significant increase in D without an increase in S at the higher stages of volume loading. During atrial contraction, increases in LA active shortening and left ventricular filling volume were limited, indicating a limited LA forward ejection. The difference between PV flow rate just before and at the end of atrial contraction increased and correlated positively with left ventricular end-diastolic pressure ($r = 0.57$, $p < 0.01$). PV flow varies according to the degree of volume loading and reflects LA functions, which exhibit limited increases in response to volume loading.

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Key Words: Pulmonary venous flow; Left atrial function; Volume loading

Recently, pulmonary venous (PV) flow, as determined by Doppler echocardiography, has been used to evaluate the diastolic properties of the left heart and to estimate filling pressure.^{1–4} It is well known that transmitral flow pattern is influenced by loading conditions.^{5–7} Although there have been some studies on the effects of loading conditions on PV flow,^{8–11} there is some confusion regarding the analysis of the relationship between left atrial (LA) dynamics and PV flow pattern.¹⁰ Kuecherer et al³ reported that the systolic fraction of PV flow, ie, the proportion of systolic velocity integral to the sum of systolic and diastolic velocity-time integral, showed a strong and inverse correlation with mean LA pressure in patients undergoing cardiovascular surgery. On the other hand, it has been reported that the ratio of systolic to diastolic PV flow rate or velocity increases as LA pressure increases in experimental volume loading studies.^{9–11}

Many factors, such as loading condition, myocardial contraction state, cardiac output, and LA functions, may affect PV flow.^{8,9} Although LA performance and PV flow may vary according to the degree of volume loading, multistaged volume loading was not performed in these studies. Moreover, although PV flow is closely related to LA pressure dynamics,² few investigators have discussed it in relation to LA functions, ie, reservoir, conduit, and booster pump functions.¹¹ We measured PV flow, LA dynamics, and left ventricular filling at a constant heart rate and examined the effects of multistaged volume loading on PV flow pattern in relation to LA functions.

Materials and Methods

Experimental Preparation and Protocol of Volume Loading

The surgical preparation has been described

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Fig 1. Recordings of electrocardiogram (ECG), left atrial pressure (LAP), left atrial dimension (LAD), and pulmonary venous flow (PVF) during volume loading.

previously.^{12,13} Briefly, 11 mongrel dogs, weighing 7.4 ± 1.7 kg, were anesthetized with intramuscular ketamine hydrochloride, 10 mg/kg, and intravenous sodium pentobarbital, 25 mg/kg, and artificially ventilated using a respirator (R-60, Aika, Tokyo). After the sinus node was ablated by right intercostal thoracotomy, right appendage pacing was performed at a rate of 100 beats/min. The pericardium was then opened widely through a left intercostal thoracotomy. The LA anteroposterior dimension and the short and longitudinal dimensions of the left ventricle were measured using a sonomicrometer (Triton Technology, San Diego, CA). The right inferior PV flow rate was measured by an electromagnetic flowmeter (MVF1200, Nihonkoden, Tokyo). LA and left ventricular (LV) pressures were measured using catheter-tip micromanometers (SPC360, Millar Instruments, Houston, TX) and lead II electrocardiograms were also recorded simultaneously. After surgical preparation, propranolol hydrochloride, 0.5 mg/kg, was administered intravenously to minimize the effects of sympathetic nerve activation.

After a stabilization period of about 30 min, 5 or 10 ml/kg of warm 6% dextran solution was infused 14 ± 2 times intravenously. During a brief interruption of artificial ventilation in the expiratory phase, the above recordings were obtained. When mean LA pressure reached as close as possible to 6, 9, 12, 15, 18 and 21 mmHg, the volume loading stage was defined as 1, 2, 3, 4, 5 and 6, respectively.

Measurements and Data Analysis

PV flow showed systolic and diastolic forward flow. During atrial contraction, PV flow rate rapidly de-

creased but the forward flow was still observed before volume loading, as described previously.^{11,12} Backward PV flow occurred during the second half of atrial contraction phase by volume loading (Fig 1). Maximum systolic and diastolic PV flow rates (S and D) were measured and the S/D ratio was calculated. PV flow rate just before atrial contraction and minimum PV flow rate or maximum backward PV flow rate at the end of atrial contraction were measured and the difference between them (Δ PVF) was also calculated.

The tracing of LA dimension showed an increase during ventricular systole, a decrease during early ventricular diastole (passive shortening), a middiastolic increase, and a second decrease during atrial contraction (active shortening). LA compliance was calculated as the ratio of dimensional increment to pressure increment between the nadir of the x descent of LA pressure and the end of the ventricular systole.

The 3 phases that were limited by the beginning of the upstroke of left ventricular pressure, the beginning of LA passive shortening, and the beginning of LA active shortening were defined as the ventricular systolic phase, the early diastolic phase, and the atrial contraction phase, respectively. The short and longitudinal dimensions of the left ventricle at the beginning and the end of each phase were also measured. Left ventricular volume was calculated from these dimensions, assuming an ellipsoid model. The longitudinal dimension of the left ventricle was analyzed as an index of mitral annulus motion.

Values are expressed as means $\pm$ standard error (SE). Statistical comparisons of the variables at various stages of the volume loading were made with an ANOVA for repeated measures. A p value less

Table 1 Left Atrial and Ventricular Performance During Volume Loading

Volume loading stage	1	2	3	4	5	6
Loading volume (ml)	6±6	90±15	180±24	272±36	348±40	409±41
Mean LAP (mmHg)	6.1±0.2	8.8±0.1	12.0±0.2	15.2±0.2	18.3±0.3	21.4±0.2
<i>Changes in LAD (mm)</i>						
LAs	2.9±0.3	3.7±0.3 ⁺	3.9±0.3 ⁺⁺	3.9±0.3 ⁺⁺	3.2±0.3	2.6±0.3
LAe	1.9±0.2	2.4±0.2	2.5±0.2	2.5±0.2	2.3±0.2	2.2±0.2
LAA	1.5±0.1	2.0±0.2 ⁺	2.3±0.2 ⁺⁺	2.3±0.2 ⁺⁺	1.9±0.2	1.3±0.2
LAC (mm/mmHg)	0.59±0.06	0.54±0.04	0.42±0.03 ^{**}	0.33±0.02 ^{**}	0.27±0.02 ^{**}	0.20±0.03 ^{**}
LVSP (mmHg)	92±7	103±6 [*]	113±6 ^{**}	116±6 ^{**}	114±6 ^{**}	113±7 ^{**}
LVEDP (mmHg)	5.2±0.4	8.5±0.5 ^{**}	13.4±0.7 ^{**}	17.7±0.7 ^{**}	20.8±0.8 ^{**}	23.3±0.8 ^{**}
LVSS (mm)	3.2±0.4	4.0±0.4	4.4±0.5 ^{**}	4.8±0.5 ^{**}	4.9±0.5 ^{**}	5.0±0.5 ^{**}
LV stroke volume (ml)	3.8±0.5	6.1±0.7 [*]	8.0±0.8 ^{**}	9.3±0.9 ^{**}	9.8±1.0 ^{**}	10.1±1.0 ^{**}
LV inflow volume (ml)						
LVe	2.4±0.3	4.1±0.4	5.6±0.6 ^{**}	6.9±0.8 ^{**}	7.7±0.8 ^{**}	8.4±0.9 ^{**}
LVa	1.4±0.2	2.0±0.3	2.4±0.3 ^{**+}	2.4±0.2 ^{**+}	2.1±0.3 [*]	1.7±0.2

LAP, left atrial pressure; LAD, left atrial dimension; LAs, left atrial dimensional increment during the ventricular systolic phase; LAe, left atrial passive shortening during the early ventricular diastolic phase; LAA, left atrial active shortening during the atrial contraction phase; LAC, left atrial compliance; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVSS, systolic shortening of LV longitudinal dimension; LV, left ventricular; LVe, LV inflow volume during the early ventricular diastolic phase; LVa, LV inflow volume during the atrial contraction phase.

* $p < 0.05$ and ** $p < 0.01$ vs stage 1: + $p < 0.05$ and * $p < 0.01$ vs stage 6.

Fig 2. Changes in maximum systolic and diastolic pulmonary venous flow rate (open and solid circles, respectively) during volume loading. *** $p < 0.01$ vs stage 1.

Fig 3. Changes in the ratio of systolic to diastolic pulmonary venous flow rate (S/D) during volume loading. + $p < 0.05$ vs stage 6

than 0.05 was considered statistically significant.

Results

Systolic PV flow rate, S, significantly increased from 189 ± 28 ml/min at stage 1 to 369 ± 52 ml/min at stage 4 and reached a plateau at stages 5 and 6 (Fig 2). LA dimensional increment during the ventricular systolic phase significantly increased from stage 1 to stage 4,

and then decreased at stages 5 and 6, indicating a limited LA reservoir function. LA compliance significantly decreased during volume loading. Stroke volume and systolic shortening of left ventricular longitudinal dimension significantly increased from stage 1 to stage 4 and reached a plateau at stages 5 and 6 (Table 1).

In contrast to S, D increased significantly and became more predominant at the higher stages of volume

Fig 4. Changes in pulmonary venous flow rate just before atrial contraction (open circles) and minimum flow rate at the end of atrial contraction (solid circles) during volume loading. * $p<0.05$ and ** $p<0.01$ vs stage 1.

Fig 5. Relationship between left ventricular end-diastolic pressure (LVEDP) and the difference between pulmonary venous flow rate just before and at the end of atrial contraction (Δ PVF).

loading (Fig 2). As for the LA dimension, passive shortening during early ventricular diastole was clearly recognized, but changes during volume loading were not statistically significant, indicating that the left atrium acts as a conduit (Table 1). D correlated with early diastolic left ventricular inflow volume ($r=0.62$, $p<0.01$).

The S/D ratio increased non-significantly from 0.87 ± 0.07 at stage 1 to 0.96 ± 0.08 at stage 3 then decreased significantly to 0.76 ± 0.08 at stage 6 because S reached a plateau whereas D continued to increase even at the higher stages of volume loading (Figs 2 and 3).

Active shortening of the left atrium and left ventricular inflow volume during atrial contraction increased from stage 1 to stage 4 but decreased at

stages 5 and 6, indicating a limited LA forward ejection (Table 1). PV flow rate just before atrial contraction increased significantly as a result of an increase in D. Δ PVF increased significantly and correlated with left ventricular end-diastolic pressure ($r=0.57$, $p<0.01$) (Figs 4 and 5).

Discussion

It is well known that the pulsatile PV flow pattern is related to LA performance? During the ventricular systolic phase, blood flow from the pulmonary vein is held in the left atrium for the next diastolic ventricular filling. When the LA dimension decreases passively during early diastole, blood flows through the left atrium, which acts as a conduit. During the atrial contraction phase, the left atrium ejects blood forward (to the left ventricle) and backward (to the pulmonary vein). In the present study, we examined the effects of multistaged volume loading on PV flow pattern in relation to LA functions.

Regarding PV flow during ventricular systole, it is known that there are many significant determinants, such as atrial contraction, LA compliance, cardiac output, and mitral valve annulus motion^{8,9,14-16}. There are conflicting data concerning the relationship between systolic PV flow and mean left atrial pressure. Kuecherer et al³ described a negative correlation between systolic PV flow velocity and mean LA pressure using transesophageal echocardiography. In contrast, systolic PV flow has been shown to increase after acute LA pressure elevation induced by volume loading⁸⁻¹¹. This discrepancy might reflect the difference in cardiac output between the volume loading state and the decreased cardiac contractile state⁹. Masuyama et al¹⁷ also showed that systolic PV flow velocity increased as cardiac index increased in patients with similar mean pulmonary capillary wedge pressure. In the present study, we demonstrated that an increase in the LA dimension during ventricular systole decreased in association with the decrease in LA compliance, the decrease in the mitral annulus motion, and the limited increase in cardiac output at the higher stages of volume loading. Thus, there is a limit to the LA reservoir function during volume loading, and this seems to result in a curvilinear increase in systolic PV flow rate.

Diastolic PV flow rate increased throughout volume loading. It has been reported that peak diastolic PV flow velocity is higher in patients with a higher pulmonary capillary wedge pressure^{16,17}. The results of our study and of clinical studies in patients with heart failure seem to agree in this respect. However, diastolic PV flow rate increased gradually in proportion to

LA pressure in this study, whereas in a clinical study by Ogawa et al¹⁶ the flow velocity suddenly increased at a certain level of pulmonary capillary wedge pressure elevation.

Actually, although the left atrium did not act as a complete conduit during diastole because of the existence of passive emptying and a mid-diastolic increase in dimension, it has been reported in previous Doppler studies that early diastolic PV flow velocities is correlated with mitral flow velocities^{2,8}. Diastolic PV flow rate correlated with left ventricular inflow volume in this study. It is also known that early diastolic mitral flow velocity increases in patients with severe heart failure (pseudonormalization¹⁸), whereas it decreases in patients with mild left ventricular dysfunction. The results of clinical studies that show a rapid increase in diastolic PV flow velocity in patients with heart failure might coexist with this pseudonormalized mitral flow pattern.

Mitral flow velocity during atrial contraction was shown to increase after volume loading in humans⁶, whereas in an experimental study it decreased at the higher stages of volume loading⁷. We also demonstrated that the pump function of the left atrium increased initially but then decreased when mean atrial pressure increased. In contrast, Δ PVF was positively correlated with left ventricular end-diastolic pressure. It is considered that LA afterload against forward ejection increases as left ventricular end-diastolic pressure increases and that "afterload mismatch of the left atrium"^{13,16,19} might be induced. Nakatani et al⁴ have also described a positive correlation between peak velocity of PV reversal and left ventricular end-diastolic pressure in patients with cardiac diseases. However, because PV flow rate just before atrial contraction depends on loading conditions, the magnitude of the waveform of PV flow might be more important than peak velocity when taking into account the LA backward ejection force.

There were several limitations to this study. First, we used an electromagnetic flowmeter, whose probe might produce artificial constriction of the pulmonary vein, to measure PV flow rate. However, we selected one with an optimum size, attached the probe carefully, and confirmed that it did not produce severe constriction after volume loading. Second, mitral regurgitation might affect PV flow at the higher stages of volume loading, but we did not observe severe regurgitation throughout the study. Finally, it should be taken into consideration that this study was performed under open-chest and open-pericardial conditions. Under closed-chest and closed-pericardial conditions, the pressure-volume curve shifts upward,

dilation of the cardiac chambers tend to be restricted, and pressure tends to increase during volume loading. Thus, left atrial reservoir function, pump function, and pulmonary venous flow may be affected in a different way by these conditions.

In conclusion, PV flow varies according to the degree of volume loading and reflects LA functions that have limited ability to respond to volume loading. Thus, the degree of loading condition as well as the myocardial contractile state should be taken into account when evaluating LA functions and left ventricular filling based on the PV flow pattern.

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