Change in Pulmonary and Systemic Circulation in Acute Ventricular Septal Defect

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SUMMARY

The correlation between left to right ventricular (L-R) shunt flow and other hemodynamic changes was studied in 16 dogs with an acute ventricular septal defect (VSD) and normal pulmonary vascular bed. The interventricular shunt flow was measured directly with a specially designed electromagnetic flowmeter probe, where the area of the VSD was constant.

The sudden presentation of VSD increased pulmonary arterial pressure, pulmonary flow and left ventricular end-diastolic pressure.

L-R shunt flow was not changed significantly by atrial pacing except when the rate was increased to over 200/min.

Dogs with a VSD were treated with isoproterenol and dextran to vary the shunt flow and hemodynamic parameters. L-R shunt flow was decreased by isoproterenol and increased by dextran loading.

The percentage changes of L-R shunt flow from pre-drug values correlated well with the change in left ventricular end-diastolic pressure ($r=0.75$) and the ratio of pulmonary to systemic vascular resistance ($r=-0.73$). Change in total pulmonary vascular resistance had a greater effect on L-R shunt flow than did a change in systemic vascular resistance, whereas a change in aortic flow had less effect ($r=0.35$) on L-R shunt flow than did a change in preload and afterload. The time to peak LV dP/dt, as an index of cardiac contractility, and heart rate were not correlated with the relative change in L-R shunt flow.

These results indicate that L-R shunt flow induced by the sudden presentation of a VSD varied with changes in the pulmonary and systemic circulation.

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L-R shunt flow in patients with VSD is determined by not only the size of the defect,[1)-3)] but also by the pulmonary to systemic vascular resistance ratio.[3)-6)] Gorlin[7)] estimated the shunt flow as the area of the ventricular defect multiplied by the square root of the mean pressure difference between the left and right ventricles. Levin et al[6)] demonstrated by cineangiography that the pressure difference between the two ventricles indicated the velocity and direction of shunt flow. These previous studies suggest that interventricular shunt flow can vary with changes in hemodynamics in conditions such as respiratory distress and exercise and with drugs in patients with a VSD. However, since there is no direct method for measuring the shunt flow clinically, little information is available about changes in shunt flow in patients with a VSD.[4)] In this study, using dogs with an experimentally produced VSD, we measured shunt flow directly with a specially designed electromagnetic flowmeter probe in order to clarify the relationship between L-R shunt flow and hemodynamic changes.

Materials and Methods

Sixteen adult mongrel dogs, weighing 10 to 13 Kg, were used. They were anesthetized by intravenous injection of 30 mg/Kg sodium thiopental, and after insertion of an endotracheal tube, were ventilated with a tidal volume of 300 ml with a positive pressure respirator (model B2, Igarashi Respirator). The heart and great vessels were exposed by midline sternotomy. A cylindrical cutter was introduced through a right ventricular purse-string suture and forced through the ventricular septum to create a perimembranous defect. A 6 mm core of septal tissue was excised from the interventricular septum with the cylindrical cutter and then a specially designed flowmeter probe (6 mm inner diameter, 8 mm outer diameter, 10 mm length, Nihon Koden) was promptly placed in the VSD as described previously.[8)] The VSD was easily opened and reclosed by a cap which was attached to threads running through the apex of the left ventricle and the free wall of the right ventricle, respectively. The position of the cutter in the interventricular septum was critical, since it was essential that the aortic valve and the chordae tendineae of the tricuspid valve not be damaged.

A suitably sized flowmeter probe (lumen diameter 10 mm or 12 mm,

Nihon Koden) was fixed in the ascending aorta for continuous monitoring of the systemic blood flow. The intracorporeal and aortic probes were connected to a square-wave electromagnetic flowmeter of constant diameter (model MF-27, Nihon Koden), which simplified determination of the minute volume. The flowmeter probe gave an accurate response when calibrated in vitro with flows of 0 to 2 l/min. The diastolic level of aortic pulsatile flow was used as a zero reference in measurement of systemic blood flow in vivo. The zero value of shunt flow was easily obtained by closing the intracorporeal probe with the cap.

Pressures were measured with Millar Instrument 4F–6F catheter-tip micromanometers, which were placed in the main pulmonary artery, right ventricle, left atrium and left ventricle. The aortic pressure was also measured by removing the catheter-tip from the left ventricle.

After production of the VSD, a period of 20–30 min was allowed for hemodynamic stabilization. When all the hemodynamic parameters were stabilized, the interventricular shunt was opened and the effects of acute L-R shunt flow on hemodynamic parameters examined as described previously.[8]

The electrocardiogram (ECG), pulmonary arterial pressure (PAP), aortic pressure (AoP), right ventricular pressure (RVP), left ventricular pressure (LVP), the first derivative of the left ventricular pressure (LV dP/dt), the aortic flow (Qs) and the velocity curve of the shunt flow (SF) were recorded on a Mingograph (model 800).

The square root of the mean pressure difference between the two ventricles, $\sqrt{(\overline{LV}-\overline{RV})PG}$, was calculated as: the square root of the mean LV pressure minus the mean RV pressure, the mean LV and RV pressures being determined electronically. The time to peak LV dP/dt (t-dP/dt) was measured as the time from the R wave of the ECG to the maximal rate of left ventricular pressure development as an index of left ventricular contractility.[9] Pulmonary flow (Qp) was calculated as Qs plus L-R shunt flow.[5),10] Systemic vascular resistance (Rs) was calculated as the mean AoP divided by Qs. Total pulmonary vascular resistance (Rp) was calculated as follows: (mean PAP−mean left atrial pressure) divided by Qp.

Five dogs served as controls for the time course, and were monitored without pharmacologic intervention for 180 min after opening the ventricular shunt.

In studies on the effect of the heart rate on ventricular shunt flow, the heart rate was changed by right atrial pacing in the range of 130 to 210 beats/min in 5 dogs with VSDs.

Another 6 dogs with VSDs were given isoproterenol at three different doses, 50, 100 and 200 ng/Kg/min intravenously for 20 min to determine the

effects of this drug on shunt flow and other hemodynamics. After the effect of isoproterenol was studied, the hemodynamic parameters were allowed to return to preinfusion values. Then, dextran was injected intravenously (100–500 ml) until mean left atrial pressure increased to 10–15 mmHg. In this experiment, 15–22 points of hemodynamic change were examined to evaluate the relation between the percentage change in L-R shunt flow and other hemodynamic parameters during isoproterenol infusion and dextran loading. In this study, hemodynamic values before isoproterenol infusion were used as control values (100%).

All results are expressed as mean values ± standard deviations. Relation between the percentage change in L-R shunt flow and other hemodynamic parameters were examined statistically by linear regression analyses. All statistical analyses were performed by the paired t-test and regression analysis. P values of 0.05 or less were considered significant.

Results

Significant hemodynamic effects were seen immediately after opening the shunt, but these stabilized within 5 min. Analysis of variance showed no significant variation in the mean AoP, mean PAP, Qs, L-R shunt flow, Rp/Rs ratio or t-dP/dt in the 180 min after opening the interventricular shunt (Fig. 1). All measurements in the animals were completed within 180 min after opening the ventricular shunt.

The effects of ventricular shunting on hemodynamics were evaluated before and 20 min after opening the shunt (Table I). The L-R shunt flow and the Qp/Qs ratio were 1.35±0.22 l/min and 2.45±0.57, respectively. These hemodynamic data showed that the dogs with experimental VSD in this study had moderate VSD with no pulmonary vascular obstruction.

Right atrial pacing did not change the L-R shunt flow and the Qp/Qs ratio except when the heart rate exceeded 200/min as shown in Fig. 2.

Tables II and III show the effects of isoproterenol and dextran infusion on the hemodynamic changes in dogs with a VSD. Isoproterenol reduced L-R shunt flow and Qp/Qs ratio significantly while increasing the Rp/Rs ratio, whereas dextran infusion increased L-R shunt flow and decreased the Rp/Rs ratio.

In individual dogs isoproterenol infusion and dextran loading varied L-R shunt flow in the range 0.37 to 2.18 l/min with changes in other hemodynamic parameters. The correlation between the percentage change in L-R shunt flow and other hemodynamic parameters are shown in Fig. 3. The percentage change in L-R shunt flow was correlated most closely with

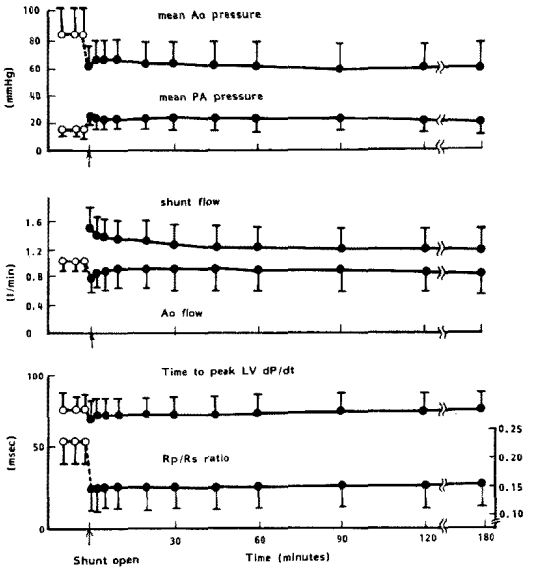

Fig. 1. Time course of changes in hemodynamic parameters before and after opening ventricular shunt. Points and bars are mean±standard deviation before (open circle) and after (closed circle) opening the shunt. n=5. Abbreviations: Ao=aorta; PA=pulmonary artery; Time to peak LV dP/dt=from the R wave of the ECG to the maximal rate of rise in left ventricular pressure as an index of left ventricular contractility.

change in the LVEDP ($r=0.75$) and the Rp/Rs ratio ($r=-0.73$). The change in L-R shunt flow was also correlated with the percentage changes in the mean AoP, Rs, mean PAP and Rp. The effect of Rp on the change in L-R shunt flow (slope$=-2.2$) was greater than that of Rs (slope$=1.3$), as determined statistically by regression analysis ($p<0.01$). The percentage change in heart rate and the t-dP/dt were not correlated with the change in L-R shunt flow.

Discussion

Quantitative data on shunt flow and the shunt flow pattern have been obtained by many methods, such as Fick's method, various indicator-dilution methods, cineangiography, echocardiography and use of the directional Doppler velocimeter. However, these methods are not sufficiently accurate and sensitive to obtain continuous data on quantitative shunt flow. To overcome these difficulties Mesel[11),12)] and Synhorst et al[13)] constructed a cannulating intracardiac transducer. The point of difference in the present procedure from that used previously[11)-13)] is the use of a cap on the intracardiac

Table I. Basic Hemodynamic Data before and after Opening the Ventricular Shunt

	close	open	p value
Heart rate (/min)	133±24	135±27	n.s.
Aortic pressure (mmHg)			
systolic	95±13	79±14	$p<0.01$
diastolic	64±14	52±10	$0.01<p<0.05$
mean	78±14	63±6	$p<0.01$
PA pressure (mmHg)			
systolic	21±5	34±8	$p<0.001$
diastolic	10±3	15±5	$p<0.001$
mean	13±3	21±5	$p<0.001$
Mean LA pressure (mmHg)	4±2	6±2	$0.01<p<0.05$
LVEDP (mmHg)	2±2	4±2	$0.01<p<0.05$
Aortic flow (l/min)	1.07±0.20	0.88±0.17	$0.01<p<0.05$
Pulmonary flow (l/min)	1.01±0.33	2.23±0.38	$p<0.001$
Shunt flow (l/min)	—	1.35±0.22	—
Qp/Qs ratio	1.0	2.45±0.57	$p<0.001$
Rp (unit)	12±3	9±3	n.s.
Rs (unit)	73±17	72±16	n.s.
Rp/Rs ratio	0.12±0.04	0.10±0.04	n.s.
t to dP/dt (msec)	58±15	60±19	n.s.

All values are mean±standard deviation, n=21.

Abbreviations: PA=pulmonary artery; LA=left atrium; LVEDP=left ventricular end-diastolic pressure; Qp/Qs=the pulmonary to systemic flow ratio; Rp=total pulmonary vascular resistance; Rs=total systemic vascular resistance; Rp/Rs=the pulmonary to systemic vascular resistance ratio; t to dP/dt=time to peak LV dP/dt.

flowmeter probe that allows closing and reopening of the interventricular shunt.

The sudden presentation of a ventricular shunt caused an increase in mean PAP, Qp and LVEDP in this study. These results are consistent with the clinical findings in patients with acute ventricular perforation secondary to myocardial infarction or trauma.[14),15)] The relative change in the LVEDP was found to be correlated with change in L-R shunt flow in the present work. The left ventricular end-diastolic volume could also be expected to be correlated with L-R shunt flow, because augmentation of Qp would increase the left atrial volume and left ventricular end-diastolic volume.[16),17)] The increased left ventricular diastolic pressure and volume might cause an augmentation of the diastolic transseptal flow and pulmonary flow in the presence of intact ventricular function.

This study also indicates that the changes in Rs and Rp were correlated with that of L-R shunt flow. Abrahamsen et al[18)] showed that injection of

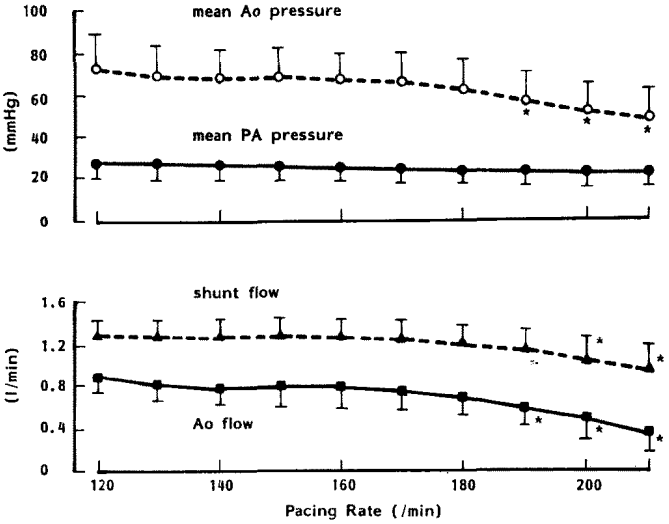

Fig. 2. Effects of atrial pacing on mean aortic pressure, mean pulmonary arterial pressure, left to right shunt flow and aortic flow. * significantly different ($p<0.05$) from the value without pacing (HR: 120/min). Points and bars are mean±standard deviation (n=5).

Table II. Effects of Isoproterenol on Left to Right Shunt Flow and Other Hemodynamic Parameters

	Isoproterenol (ng/Kg/min)			
	zero	50	100	200
Heart rate (/min)	123±15	132±13	134±18	137±20
Mean Ao P (mmHg)	66±7	66±12	65±17	61±20
Mean PA P (mmHg)	26±4	24±4	24±4	23±4
Mean LA P (mmHg)	6±2	6±2	5±2	4±2*
LVEDP (mmHg)	4±2	3±2	3±1	2±1*
$\sqrt{(\overline{LV}-\overline{RV})PG}$ (mmHg)	6±1	6±1	6±1	6±1
Ao flow	1.02±0.22	1.25±0.31**	1.28±0.36**	1.40±0.20**
PA flow	2.27±0.42	2.05±0.40	1.98±0.37	1.98±0.44
Shunt flow (l/min)	1.25±0.35	0.80±0.22	0.70±0.24*	0.58±0.20**
Qp/Qs ratio	2.23±0.34	1.64±0.22*	1.55±0.23**	1.41±0.17**
Rp (unit)	11±2	12±2	12±2	12±2
Rs (unit)	65±10	53±12	51±12*	44±18**
Rp/Rs ratio	0.14±0.02	0.17±0.03	0.19±0.05*	0.22±0.05**
t to dP/dt (msec)	55±6	50±6	49±5	46±5*

All values are mean±standard deviation. n=6. *, ** significant difference between before and after isoproterenol infusion (* $0.01<p<0.05$, ** $p<0.01$).

Table III. Effects of Dextran Infusion on Left to Right Shunt Flow and Other Hemodynamic Parameters

	before	after	p value
Mean LA P (mmHg)	6±2	12±4	<0.05
Heart rate (/min)	126±17	103±15	<0.05
Mean Ao P (mmHg)	65±7	88±9	<0.01
Mean PA P (mmHg)	24±5	29±5	n.s.
LVEDP (mmHg)	4±2	7±3	n.s.
$\sqrt{(\overline{LV}-\overline{RV})PG}$ (mmHg)	6±1	5±1	n.s.
Ao flow (l/min)	1.05±0.27	1.21±0.25	n.s.
PA flow (l/min)	2.21±0.33	2.75±0.36	<0.05
Shunt flow (l/min)	1.16±0.27	1.54±0.30	<0.05
Qp/Qs ratio	2.10±0.27	2.27±0.31	n.s.
Rp (unit)	10±2	6±2	<0.01
Rs (unit)	62±12	73±13	n.s.
Rp/Rs ratio	0.15±0.03	0.09±0.03	<0.01
t to dP/dt (msec)	54±5	62±7	<0.05

All values are mean±SD, n=6.

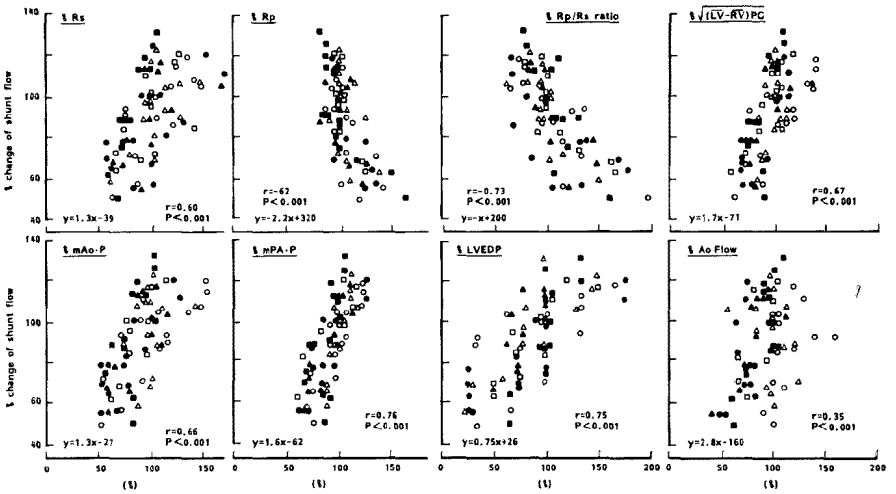

Fig. 3. Relationship between hemodynamic changes (horizontal axis) and left to right shunt flow (vertical axes). Different symbols (○ □ △ ● ■ ▲) indicate values in different dogs. %=percentage change in each hemodynamic parameter from the value before drug infusion.

methoxamine increased L-R shunt flow in a patient with a VSD. Conversely, hydralazine decreased the Qp/Qs ratio in all patients with VSD and high Rs.[19),20)] Experimental studies in dogs with VSD have shown that phen-

tolamine, isoproterenol and isosorbide dinitrate can decrease L-R shunt flow.[2),7),21)] These previous findings and this present paper indicate that L-R shunt flow depends primarily on Rs and Rp. Moreover, this study showed that the change in Rp has a greater effect on L-R shunt flow than does a change in Rs. Moreover, Rp should play a more important role in patients with high Rp.

On application of Gorlin's formula to data obtained in the present study, L-R shunt flow should be directly proportional to the square root of the mean pressure difference between the two ventricles ($r=1$, slope$=1$), since the area of the ventricular defect was constant in this study. However, the correlation coefficient and slope in this study were only 0.60 and 0.58, respectively. These results indicate that the square root of the mean pressure difference between the two ventricles is not an accurate measure of the mean interventricular shunt flow velocity. This may be because the square root of the mean pressure difference is not the same as the mean of the integral of the square root of the instantaneous pressure differences between the two ventricles. Another possibility is that the pressure-flow relation between the two ventricles is affected by not only their pressure difference but also by the ventricular volume and properties of the muscle such as cardiac contractility and elasticity.

The correlation between cardiac contractility and interventricular shunt flow has not been studied. An ideal index for assessing cardiac contractility should not be affected by changes in heart rate, preload or afterload, and should reflect only the inotropic state of the myocardium. No such ideal index has been found for patients with VSD. T-dP/dt, an index of cardiac contractility, was not correlated with L-R shunt flow in this study. And, while it remains unclear as to how positive inotropism affects L-R shunt flow, isoproterenol has been used as an emergency measure to increase contractility in infants with VSD and severe heart failure.[3)] Increase in cardiac contractility may augment Qs with a decrease in L-R shunt flow and improve the filling pressure of the left ventricle in those patients with a VSD and congestive heart failure.

It is concluded from the present work that L-R shunt flow in patients with VSD is changeable, and depends on many hemodynamic factors, such as the LVEDP, Rp/Rs ratio, Rs, Rp and the square root of pressure difference between the two ventricles, but not on the heart rate or t-dP/dt.

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