Functional and Geometrical Interference and Interdependency between the Right and Left Ventricle in Cor Pulmonale: An Experimental Study on Simultaneous Measurement of Biventricular Geometry of Acute Right Ventricular Pressure Overload

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To clarify the effects of right ventricular (RV) pressure overload on functional and geometrical interference and interdependency between the right and left ventricle, both ventricular internal diameters were measured by the microcrystal technique during lycopodium induced pulmonary embolization in the dog. By repeated embolization, RV systolic pressure was increased progressively until it reached a peak value of about 60–70 mmHg, then it began to fall. At the same time, the hemodynamics deteriorated progressively resulting in death. During the experiment, gradual leftward displacement of the interventricular septum (IVS) without any change in left ventricular (LV) free wall geometry was observed. In pulmonary embolic shock, which showed a fall in LV pressure to about 60 mmHg and cardiac output to about 40% of control, the leftward displacement of IVS became marked, and the cooperative movement of IVS to LV contraction disappeared. The IVS position during acute RV pressure overload was able to account for the transseptal pressure gradient. The importance of IVS position and motion in cardiac function during acute RV pressure overload was stressed.

Furthermore, to establish the theoretical treatment in acute cardiopulmonary resuscitation, ligation of the descending aorta (AoL) or norepinephrine ("N") or isoproterenol ("I") administration were examined in a canine pulmonary embolic shock model. AoL or "N" improved the deteriorated hemodynamics with restoration of biventricular geometry. However, "I" did not restore the biventricular geometry despite the transiently improved hemodynamics, and the experimental animals were unable to survive. These results suggest the importance of the maintenance of systemic pressure for the restoration of failed RV function. Further integrated studies are required to understand biventricular interference and interdependency.

Key words:
Cor pulmonale
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Ventricular Geometry
Ventricular function
Ventricular interference

In cor pulmonale, it is still controversial as to whether or not a concomitant disturbance of the left ventricular (LV) function is due to right side failure. Recently, clinical and experimental studies on right ventricular (RV) pressure overload have shown that the shape of both ventricles is altered as a result of a leftward displacement of the septum from its...
normal position. These findings have served to focus attention on the role of the interventricular septum (IVS) in mediating ventricular interaction. Although several mechanisms have been postulated to explain the ventricular function in RV pressure overload especially with regard to the serial effect through pulmonary circulation and the direct mechanical coupling through IVS and common muscle fibers belonging to the bilateral ventricles, no systematic study by simultaneous observation of both ventricular diameters has been previously undertaken, especially while preserving the pericardium.

Recently we have devised a new technique for the simultaneous measurement of biventricular septal-to-free wall diameters employing ultrasonic microcrystals. This technique allows for reliable analysis of interference and interdependency between the right and left ventricle in detail.

The purpose of the present study was to clarify the effects of right ventricular pressure overload on functional and geometrical interference and interdependency between the right and left ventricle. Furthermore an attempt was made to investigate the effects of some mechanical and pharmacological interventions on pulmonary embolic shock in order to re-evaluate the rationale for conventional therapeutic procedure.

MATERIAL AND METHODS
Twenty four adult mongrel dogs weighing 9 to 18 kg (average 12.1) were anesthetized with sodium pentobarbital (25 kg/kg i.v.). After endotracheal intubation, ventilation was maintained by a volume respirator (Harvard Model 607) with room air. A transternal thoracotomy was performed in each dog in the fifth intercostal space.

Placement of the ultrasonic crystals
As shown in Fig. 1, three pairs of ultrasonic crystals (5 mm in diameter) were placed on the biventricular endocardial surfaces, through the bilateral atrial appendages by making small incisions in the pericardium. Details of the placement technique have been described elsewhere. Briefly, small incisions were made on the right and left appendage with minimal incision of the pericardium. A pair of snares was inserted through each appendage into the ipsilateral ventricular cavity. A 13 cm-long fine needle with doubled fishing gut was inserted and transfixed along the left ventricular maximal transverse diameter from the center of the right ventricular free wall to the left ventricular lateral wall through the snare rings in the ventricles. The loops of the fishing gut in the ventricles were then drawn out through the appendage, using the snares. The loops of the gut were cut off, then the end of each string was bound with each end of two pairs of microcrystal transducers. By withdrawing the free end of the guts, each transducer was pulled into the ventricular cavities and placed on both sides of the interventricular septum and the ventricular free wall. For
measuring anterior-posterior diameters of the left ventricle, the third pair of transducers was placed on the endocardial surfaces using another needle with gut and another single snare inserted into the left ventricle.

After these procedures, the septal-to-free wall diameters of the right and left ventricle (RVD and LVD, respectively) could be measured in a straight line. The anterior-posterior diameter of the left ventricle (LVAP) was measured perpendicular to the aforementioned transverse axis. The ultrasonic signals were continuously monitored with a four channel ultrasonic dimension system (Medirand Inc., UDM-59). The instantaneous change in distance between the crystals was calculated according to the velocity of sound in blood (1.5 \times 10^5 \text{ cm/sec.})

**Measurements of hemodynamics**

Two micromanometer-tipped catheters (Millar Instruments, MPC-500) were inserted into either ventricle through the apical portion of each ventricle, with minimal incision in the pericardium, for simultaneous measurement of the biventricular pressures. An electromagnetic flow probe was placed either around the main pulmonary arterial trunk or the ascending aorta through a small incision in the pericardium for measuring the cardiac output (CO) (Nihon-Kohden, Model MFV 1200). After the instrumentation, the incisions in the pericardium were closed loosely with sutures, taking care not to restrict the heart. Hemodynamic data was recorded on an 8 channel recorder (Nihon-Kohden multipurpose polygraph, Model RM-85) together with the data on the ventricular geometry.

**Experimental protocol**

In the first experiment, we examined changes in the biventricular hemodynamics and geometry during experimental acute RV pressure overload in 6 dogs. For this purpose, an increase in RV afterload was induced by pulmonary microembolism with repetitive injection of 0.2 to 1.0 ml of physiological saline suspension of lycopodium spores (50 mg/ml). Hemodynamic and ultrasonic data was obtained in the control and at each stage of RV pressure overload (PH-1 = 30 < RVSP < 40, PH-2 = 40 < RVSP < 50, PH-3 = 50 < RVSP < 60, max-PH = maximal RVSP, late-PH = the stage of pulmonary embolic shock; RVSP = RV systolic pressure: mmHg).

In the second experiment, the effect of three types of intervention during acute pulmonary embolic shock were studied in three groups. Each group consisted of 6 dogs. These were 1) ligation of the descending aorta (AoL), 2) repetitive injection of norepinephrine 100 \mu g and 3) repetitive injection of isoproterenol 200 \mu g, for
recovering the reduced LVSP to the control level.

Data analysis:
All pressures and diameters were measured manually in the control and during the experimental period for each intervention. For the statistical analysis, we used Student’s t-test, and a p < 0.05 was considered significant.

RESULTS

Hemodynamic and geometric changes in the first experiment
Figure 2 shows representative recordings from a typical experiment of acute RV pressure load imposed by lycopodium pulmonary embolization. The mean hemodynamic and geometric data obtained in the first experiment are shown in Fig. 3. The repetitive embolization increased RVSP and right ventricular end-diastolic pressure (RVEDP) stepwise with a gradual decrease in LVSP, left ventricular end-diastolic pressure (LVEDP) and CO before RVSP reached maximum. Further embolization decreased RVSP, at the same time LVSP, LVEDP and CO were decreased and RVEDP was elevated.

With biventricular geometry, LVD was decreased with simultaneous RVD increase (leftward displacement of IVS), whereas LVAP showed no significant change. When the RVSP reached maximum, the leftward displacement of IVS became evident. During the late stage of embolism, leftward displacement of IVS became more marked and systolic shortening of LVD diminished. If no treatment was undertaken, and the animal was left in that condition, LVD was
Fig. 4. Representative tracings obtained from three types of intervention in pulmonary embolic shock. Fig. 4a shows the effect of ligation of the descending aorta (AoL), Fig. 4b shows the effect of norepinephrine injection and Fig. 4c shows the effect of isoproterenol injection.

Fig. 5. Effects of three types of intervention on hemodynamics and biventricular geometry. Left panel shows mean hemodynamic values and right panel shows biventricular diameters during control, severe pulmonary hypertension and immediately after each intervention for pulmonary embolic shock. C = control; S-PH = pulmonary embolic shock; Treat = after each intervention; Ao = ligation of the descending aorta; N = norepinephrine injection; I = isoproterenol injection; * = p < 0.05, Other abbreviations were similar to Fig. 3.

decreased further in diastole with a marked increase in RVD, LVD then was increased in systole.

*Hemodynamic and geometric changes before and after the three types of intervention in pulmonary embolic shock*

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Figure 4 shows representative recordings from a typical experiment with AoL (Fig. 4a), nor-epinephrine injection (Fig. 4b) and isoproterenol injection (Fig. 4c) during pulmonary embolic shock, and the mean hemodynamic and geometric data obtained in the second experiment are shown in Fig. 5. With each treatment, LVSP was elevated initially, with some elevation of RVSP in each group. Although the elevated LVSP was maintained as long as AoL or nor-epinephrine therapy continued, LVSP was not maintained by isoproterenol administration alone. Under these circumstances, RVEDP was decreased and approached the control level in each intervention, LVEDP was elevated by AoL or nor-epinephrine administration and was decreased by isoproterenol administration. Sonomicrometry revealed LVD increase with RVD decrease throughout the whole cardiac cycle in the AoL or nor-epinephrine groups and both leftward displacement of IVS and systolic shortening of LVD were improved. However, in the isoproterenol group, leftward displacement of IVS remained unchanged and finally ventricular contraction failed with hemodynamic deterioration.

DISCUSSION

So far, many investigators have examined ventricular function and/or geometry using ultrasonic crystals, but the majority measured only one side of a pair of ventricles, and there are few reports of simultaneous measurement of biventricular geometry. This may be due to two problems: the first problem is the theoretical background necessary to evaluate RV function, and the second is a technique for placing microcrystals on the endocardial surface of the ventricles while preserving the pericardium. We considered the LV contraction to be a concentric movement toward the center of the LV cavity and RV contraction as a bellows action of the RV free-wall toward IVS. We measured the RV septal-to-free wall diameter (RVD), LV septal-to-free wall diameter (LVD) and LV anterior-posterior diameter (LVAP) as represented in Fig. 1. For placing microcrystals, we developed a new insertion technique via the bilateral atrial appendages. Using this new method, each microcrystal was placed at the optimal point on the biventricular endocardial surface while preserving the pericardium. Reliable signals could then be obtained throughout the experiment.

In the first step of this experiment, the hemodynamics were changed as in previous studies during incremental RV pressure overload induced by pulmonary artery embolism. The right ventricle became enlarged and biventricular figure was changed, especially by leftward displacement of IVS.

Concerning RV function, some investigators measured RV free-wall segment length (RVSL) during RV pressure overload. It was reported that RVSL stretched in end-diastole and developed higher RV pressure (Frank-Starling's law) during RV overload than in the control, though this stretching was only an 8 to 10 percent increase of the initial myocardial length. The present study showed more apparent changes in RVD than RVSL during RV pressure overload, which suggested that RV function should be evaluated not only by RV free wall but also RVD.

Concerning LV function, LVD was decreased gradually with reduced systolic excursion of IVS into the LV cavity during RV pressure overload. In the final stage of embolism, marked falls in CO, LVSP, RVSP and LVEDP were observed with significant elevation in RVEDP. During this period, IVS was diverted deeply into the LV cavity at end diastole, and cooperative systolic shortening of LVD was no longer able to be observed. In the present study, un-cooperative systolic movement of IVS resulted in immediate hemodynamic deterioration. On the other hand, LVAP showed no significant change throughout the whole cardiac cycle during the experimental period. These results suggested that the LV free-wall works normally even in the failure of IVS, whose position and motion are important factors in keeping LV function less deranged during RV pressure overload.

In the second step, we examined three types of intervention for pulmonary embolic shock while measuring biventricular geometry. So far there have been many studies of the acute cardiopulmonary effects of pharmacological treatment of pulmonary hypertension caused by pulmonary embolism. Norepinephrine, isoproterenol, vasodilating agents, volume adjusting overload and fibrinolytic therapy have been tried. Among them, cardiotoxic agents are usually preferable in acute circulatory failure and shock. Although some previous
studies have been done to evaluate the usefulness of these therapeutic trials hemodynamically studies involving simultaneous measurement of biventricular geometry have not been performed. In our studies, AoL and norepinephrine improved biventricular geometry with hemodynamic improvement. Isoproterenol, however, did not alter biventricular geometry which had been strongly affected by the leftward displacement of IVS. Furthermore, although all dogs treated with AoL and norepinephrine were hemodynamically stable during each treatment, all those treated with isoproterenol died subsequently as a result of hemodynamic deterioration. Concerning intraventricular pressure, AoL and norepinephrine decreased the already elevated RVEDP with the increase of LVdP. As a result, the negative value of end-diastolic transseptal pressure improved. However, isoproterenol decreased RVEDP with the further decrease in LVdP, in this situation transseptal pressure remained negative. These data probably account for the difference in the effects of isoproterenol from norepinephrine, and also from AoL, on the position and motion of IVS in pulmonary embolic shock.

In short, although isoproterenol revealed inotropic action initially with the increase in CO, ventricular contractility and heart rate, it did not show the desired result in pulmonary embolic shock.

Salisbury demonstrated that RV failure could be improved by aortic constriction and suggested that myocardial perfusion may influence the ability of RV to pump against increased afterload. Brooks et al demonstrated that experimental RV failure improved when right coronary perfusion pressure was increased. On hemodynamic and biochemical effects, Vlahakes et al investigated a canine model with acute RV hypertension, and explained RV failure by ischemia as detected by biochemical analysis of ventricular biopsies. These results suggest that, under similar conditions, aortic compression, hyper-perfusion of the right coronary artery and administration of the pressor agents may have produced beneficial hemodynamic effects, presumably by relieving RV ischemia.

We have reported the effects of isoproterenol and norepinephrine on the coronary blood flow in pulmonary embolic shock. Although norepinephrine increased right and left coronary flow simultaneously during systole and diastole, isoproterenol increased only diastolic coronary flow with reverse flow in systole in the right and left coronary arteries. In the control condition of the preliminary experiment, isoproterenol induced reverse coronary flow during systole only in the left coronary artery, and induced newly systolic reverse flow in the right coronary artery during pulmonary embolic shock. As for systolic reverse flow in the left coronary artery, Kajiya et al also described the existence of excessive intramyocardial pressure with reduced coronary perfusion pressure during isoproterenol infusion. There was also a mismatch between right ventricular intramyocardial pressure and coronary perfusion pressure during isoproterenol treatment for pulmonary embolic shock. Because of systolic reverse flow, the increment of the diastolic coronary flow was cancelled and total coronary blood flow was increased to a lesser degree during isoproterenol infusion than norepinephrine infusion.

Recently, Molloy et al investigated the acute cardio-pulmonary effects of norepinephrine and isoproterenol in a canine model with pulmonary embolism. They suggested that isoproterenol is the preferred agent for treatment of acute pulmonary embolism without shock. In another article, they noted that norepinephrine is superior to isoproterenol for acute resuscitation from embolic shock. Our present result coincides with the second study findings. That is, in a canine model with pulmonary embolism and shock, the elevation of systemic blood pressure restored biventricular geometry and function. We consider that an improvement in myocardial ischemia is one of the most important factors in the restoration of failed RV function.

Consequently, during RV pressure overload, present results indicate some limitation in LV function through RV dilatation with leftward shift of IVS, and a simultaneous dependency of RV function on LV function, aortic pressure and coronary perfusion. Further integrated clinical studies are required to confirm the biventricular function for the establishment of theoretical treatment of RV failure including cor pulmonale.

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