Right Ventricular Function Under Acute Cor Pulmonale

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Many investigators have reported the hemodynamics in acute cor pulmonale clinically and experimentally. However, earlier studies have not made quantitative evaluations of the effects of coronary perfusion pressure and hypoxia on right ventricular contractility. We simulated acute cor pulmonale in nine isolated canine hearts and investigated the relationship of the process to cardiac deterioration and restoration.

The afterload and preload of the right ventricle were controlled with a computer-assisted load control servosystem. Coronary perfusion pressure (COPP) was also controlled at either normal or variable levels identical to products of measured cardiac output and assumed values of systemic vascular resistance. Critical state (CS) was defined as a condition with an initial decrease in peak systolic pressure despite increased afterload.

Within the normal range of PaO_2 (105 ± 5.3 mmHg), CS developed at a COPP of 51 ± 5.1 mmHg, while under low PaO_2 (51 ± 2.3 mmHg), it developed at a COPP of 59 ± 8.8 mmHg. As long as the COPP was normal (90 mmHg), the contractility of the right ventricle did not decrease despite hypoxia (PaO_2 51 ± 2.3 mmHg).

An increase in systemic vascular resistance or administration of a beta-stimulant at CS restored the contractility of the right ventricle. However, an increase in preload decreased the contractility of the right ventricle.

IN massive pulmonary embolisms, about 75% of deaths develop within 1 hour after the onset. Therefore, the mechanism of this acute deterioration has not been clarified in detail. Many investigators have reported the hemodynamics in acute cor pulmonale clinically or experimentally^{1,2}. However, quantitative studies on each effect of increased afterload, hypoxia, and decreased coronary perfusion pressure on cardiac functions, which are the principal conditions in acute cor pulmonale, have not been performed sufficiently, since these conditions

develop simultaneously in vivo. In the present study, we investigated these effects on cardiac functions separately, and together, by simulating acute cor pulmonale in isolated hearts using a microcomputer controlled servosystem to clarify the process of cardiac deterioration and to obtain informative guide for treatment.

METHOD

Nine pairs of mongrel dogs weighing 8–20 kg were used. Each pair was anesthetized with sodium pentobarbital (25 mg/kg i.v.). The chest of the smaller dog in the pair was opened under artificial ventilation. The brachiocephalic artery and superior vena cava were cannulated and connected to the carotid arteries and vein, respec-

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Fig.3. Representative changes of right ventricular pressure-volume loops in a single heart by low coronary perfusion pressure and/or hypoxia.

Left panel: solid line and broken line show end-systolic pressure-volume relationships (ESPVR), lines tangent to left upper corners of each set of pressure-volume loops, under normal coronary perfusion pressure (COPP) of 90 mmHg with normal PaO_2 (98 mmHg), and with decreased PaO_2 (50 mmHg), respectively. There is little difference between slopes (E_{max}) of the two ESPVR lines. Middle panel: solid line indicates the same ESPVR as control one in the left panel. Broken line indicates ESPVR under COPP dependent on cardiac output with normal PaO_2 . Point A indicates where slope of ESPVR line declined compared with control line, while point B indicates where systolic pressure decreased despite an increase in pulmonary vascular resistance. COPP at A point and B point were 61 mmHg and 46 mmHg, respectively. Right panel: solid line indicates ESPVR under constant COPP of 90 mmHg with decreased PaO_2 (50 mmHg) as a control. Broken line shows ESPVR under COPP dependent on cardiac output with decreased PaO_2 . COPP at point A and point B were 69 mmHg and 58 mmHg, respectively.

resistance. This command was outputted to the servo pump system via a 12 bit D/A converter at a real time from a microcomputer also controlling ventricular loading.

The right atrium was opened and the chordae tendineae were severed. A metal ring was sutured to the tricuspid annulus. Vents were placed in the apices of both ventricles for drainage. A thin balloon connected to a Bellofram cylinder via a rigid plastic tube was placed inside the right ventricle through the metal ring. The volume of the right ventricle was measured by a position sensitive detector and controlled by the Bellofram cylinder driven by a linear motor.

Right ventricular pressure was measured by a micromanometer (Kongsberg P7) placed inside the balloon through a stab incision at the apex of the right ventricle. The pressure was digitized at 1 kHz using 12 bit A/D converter, and inputted to the microcomputer (CPU 8086 with numeric data processor 8087). Instantaneous right ventricular volume was calculated at a real time based on the assumed right ventricular preload and afterload model, and was outputted to the volume control servo-system via a 12 bit D/A

converter (volume resolution 0.03 ml). The afterload consisted of pulmonary vascular resistance, pulmonary artery compliance, characteristic impedance, and inertia of blood (Fig. 2). Details of this system have been reported elsewhere.³ The pressure-volume loops were displayed on a CRT at real time with a 16 bit personal computer (PC 9801, NEC) by sampling them at 500 Hz via a 12 bit A/D converter and drawn on a plotter.

The partial oxygen pressure (PaO_2) of the arterial blood flowing into the isolated heart was measured with a blood gas analyzer (Corning 168). When the PaO_2 decreased spontaneously, we maintained the PaO_2 in the normal range (90–120 mmHg) by giving oxygen to the support dog. In hypoxic studies, PaO_2 was decreased to about 50 mmHg by mixing an appropriate amount of venous blood from the femoral vein of the support dog with the arterial blood.

PROTOCOL

We recorded right ventricular pressure-volume loops and obtained end-systolic pressure-volume

TABLE I EFFECTS OF HYPOXIA ON RIGHT VENTRICULAR FUNCTIONS IN NINE HEARTS

	E_{max} (mmHg·ml ⁻¹)	COPP (mmHg)		SV (%)		SP (%)		PVR (mmHg·sec·ml ⁻¹)	
		A	B	A	B	A	B	A	B
PaO ₂ normal (105 (5) mmHg)	7.3 (5.6)	64 (7)	51 (5)	74 (10)	57 (6)	130 (15)	126 (18)	4.3 (1.5)	5.4 (1.4)
PaO ₂ decreased (51 (2) mmHg)	6.9 (5.3) N.S.	72 (4)**	59 (9)*	84 (9)**	68 (10)*	114 (14)*	113 (18) N.S.	3.2 (1.1)**	4.1 (1.4)**

Values are mean (SD).

A: the point where the slope of ESPVR line declined compared with the control line. B: the point where the right ventricular systolic pressure decreased despite increase in PVR. COPP = coronary perfusion pressure; SV (%) = percent of right ventricular stroke volume at PVR of 2.0 mmHg·sec·ml⁻¹; SP (%) = percent of right ventricular systolic pressure at PVR of 2.0 mmHg·sec·ml⁻¹; PVR = pulmonary vascular resistance.

*; $p < 0.05$, **; $p < 0.01$, N.S.: not significant compared with the value at normal PaO₂.

relationships (ESPVR)^{4,5} by increasing pulmonary vascular resistance from 2.0 mmHg/ml/sec to 20.0 mmHg/ml/sec stepwise under the following conditions.

1) Normal PaO₂ (90–120 mmHg), constant COPP (90 mmHg)

2) Decreased PaO₂ (50–60 mmHg), constant COPP (90 mmHg)

3) Normal PaO₂, COPP dependent on cardiac output (i.e. COPP calculated with measured cardiac output and assumed systemic vascular resistance)

4) Decreased PaO₂, COPP dependent on cardiac output Right ventricular end-diastolic pressure (RVEDP) was initially set to 10 mmHg, and systemic vascular resistance was adjusted for an initial COPP to be 90 mmHg under control cardiac output through experiment 3) to 4).

We defined "critical state, CS" as a beginning of a vicious circle, when right ventricular systolic pressure decreased despite an increase in pulmonary vascular resistance through a decrease in COPP in experiments 3) and 4). When CS developed, we tried the following therapeutic maneuvers, and then analyzed the recovery process from CS.

a) Stepwise increase in RVEDP from 10 mmHg to 35 mmHg

b) Increase in systemic vascular resistance two times of the initial value

c) Administration of dobutamine (bolus injection about 400 µg into the arterial line supporting an isolated heart) Throughout this report, variation of the data is given in terms of one standard deviation of the mean. The significance of differences between values was examined by the paired t test and differences giving a $p < 0.05$ were regarded as significant.

RESULTS

Effects of hypoxia and/or COPP on right ventricular ESPVR

Figure 3 shows representative right ventricular pressure-volume loops from one heart. In the left panel, the solid line indicates the right ventricular ESPVR obtained by a stepwise increase in pulmonary vascular resistance under constant COPP (90 mmHg) with normal PaO₂ (98 mmHg) as a control. The broken line indicates the ESPVR under constant COPP (90 mmHg) with decreased PaO₂ (50 mmHg). There is little difference between the slopes (E_{max}) of the two ESPVR lines. The ESPVR line shifted to the left

Fig.4. Representative effects of various therapies on right ventricular systolic functions in one heart in critical state.

From left to right, increase of right ventricular end-diastolic pressure (RVEDP), increase of systemic vascular resistance (SVR), and administration of dobutamine. Left panel: with an increase in RVEDP, contractility represented by slope of ESPVR line (broken line) decreased, although stroke volume slightly increased. Middle panel: with an increase in SVR, both stroke volume and contractility increased. Right panel: with an administration of dobutamine, both stroke volume and contractility markedly increased.

Fig.5. Effects of therapies on right ventricular functions in nine hearts.

From left to right, increase in right ventricular end-diastolic pressure (RVEDP), systemic vascular resistance (SVR), and administration of dobutamine. Left panel: when RVEDP was increased from 10 mmHg to 15 mmHg and from 20 mmHg to 25 mmHg, stroke volume significantly increased, while $dp/dt/p$ significantly decreased. Middle panel: with an increase in SVR, stroke volume increased significantly while $dp/dt/p$ did not change significantly. Right panel: with administration of dobutamine, both stroke volume and $dp/dt/p$ increased significantly. Small bars are standard deviation of mean. *, $p < 0.05$; **, $p < 0.01$.

with decreased PaO_2 .

In the middle panel, the solid line indicates the same ESPVR as the control one in the left panel. The broken line shows the ESPVR under COPP dependent on cardiac output with normal PaO_2 . We defined point A as the point where the slope of ESPVR line declined compared with the control line. And we defined point B as the point where the right ventricular systolic pressure decreased in spite of an increase in pulmonary

vascular resistance (CS). The COPP at point A and point B were 61 mmHg and 46 mmHg, respectively.

In the right panel, the solid line indicates the ESPVR under constant COPP of 90 mmHg with decreased PaO_2 (50 mmHg) as a control. The broken line indicates the ESPVR under decreased PaO_2 and COPP dependent on cardiac output. The COPP at point A and point B were 69 mmHg and 58 mmHg, respectively.

Fig.6. Radiological confirmation of accuracy in the volume measurement in right ventricle by the present method.

A thin latex balloon for volume measurements was filled with radiological contrast. Photographs in the two directions, anteroposterior (AP) and lateral (LAT), were taken at the pressure of 20 mmHg in the balloon. PV, pulmonary valve; TV, tricuspid valve. Right ventricular outflow tract was filled up to pulmonary valve, and apical region was also filled without any remaining space.

Table I summarizes various effects of hypoxia on right ventricular functions in nine hearts. There was no significant difference between the E_{max} at normal PaO_2 and the one at decreased PaO_2 . At point A, the COPP and percent of right ventricular stroke volume at pulmonary vascular resistance of 2.0 mmHg/ml/sec at decreased PaO_2 were significantly higher than those at normal PaO_2 . The percent of peak systolic pressure at pulmonary vascular resistance of 2.0 mmHg/ml/sec and pulmonary vascular resistance at decreased PaO_2 were significantly lower than those at normal PaO_2 . At point B, the COPP and stroke volume at decreased PaO_2 were significantly higher than those at normal PaO_2 . The pulmonary vascular resistance at decreased PaO_2 was significantly lower than the one at normal PaO_2 . However, systolic pressure at normal PaO_2 and at decreased PaO_2 did not show any significant differences.

Effects of increasing preload, systemic vascular resistance for restoration of coronary perfusion pressure, and administration of dobutamine on the critical state

Figure 4 shows representative effects of therapies on CS, which was defined as a decrease in peak systolic pressure despite an increase in

Fig.7. Effects of left ventricular loading state on right ventricular functions.

Representative right ventricular pressure-volume loops in one heart are shown. Loops 1, 2 and 3 are obtained under the following conditions: 1, left ventricle without any load; 2, LVEDP of 20 mmHg with a very low afterload; 3, LVEDP of 20 mmHg with the maximum afterload (isovolumic contraction). The left upper corner of the loops moved to the upper left slightly with an increase in LVEDP and further with an increase in afterload.

pulmonary vascular resistance. The left panel shows the effects of an increase in RVEDP. Although stroke volume increased slightly, contractility decreased, i.e. the slope of the ESPVR line decreased with an increase in RVEDP, and external works, represented by areas surrounded by pressure volume loops, apparently decreased along with an increase in preload.

The middle panel shows the effects of an increase in systemic vascular resistance. Both stroke volume and contractility increased, i.e. end-systolic point shifted toward the upper left under a constant preload and afterload. The right panel shows the effects of dobutamine administration. Both stroke volume and contractility markedly increased.

Figure 5 summarizes the effects of therapies on right ventricular functions in 9 hearts. They were examined on stroke volume and $dp/dt/p$. The small bars in Fig. 5 show standard deviations of the mean. The left panel shows the effects of an increase in RVEDP. When the

RVEDP was increased from 10 mmHg to 15 mmHg and from 20 mmHg to 25 mmHg, stroke volume significantly increased, but $dp/dt/p$ significantly decreased. The middle panel shows the effects of an increase in systemic vascular resistance. Stroke volume increased significantly, but $dp/dt/p$ did not change. The right panel shows the effects of dobutamine administration. Both stroke volume and $dp/dt/p$ increased significantly.

DISCUSSION

Methodological Considerations

The principal hemodynamic effects of massive pulmonary embolism consists of 1) increase in pulmonary vascular resistance, 2) decrease in aortic pressure and COPP due to a decrease in right ventricular and left ventricular cardiac output, and 3) hypoxia. In earlier studies of pulmonary embolism with hearts in situ, the effect of each of these conditions on right ventricular function has not been assessed separately, since these conditions develop simultaneously in situ.

The present system has the following advantages. First, unlike in vivo studies, the above conditions can be controlled separately, and also in any combination, simultating in situ. Second, interventions can be repeated with precise controls of parameters after initial state is restored in a short time. Therefore, it allows us to assess effects on the same heart quantitatively and compare them easily. Third, the parameters used in earlier studies to assess right ventricular functions have problems, because such parameters as systolic pressure, stroke volume or shortening fraction are dependent on preload and afterload. These problems make it necessary to use the relationship between pressure and volume. However, it is difficult to measure right ventricular volume accurately in situ because of its complex geometry. The present method uses a thin latex balloon to overcome this difficulty. This balloon filled up the entire right ventricular cavity including the outflow tract and apical region as shown in Fig. 6, and ascertained an accurate measurement of volume.

We simulated pulmonary embolism by increasing only pulmonary vascular resistance without a decrease in pulmonary vascular compliance. This simplification is based on our observation that a decrease in pulmonary vascular compliance affects right ventricular stroke volume far less than an increase in pulmonary vascular

resistance.

In the present experiment, we investigated right ventricular functions with unloaded left ventricle, and some differences may exist between our results and those in situ. Effects of left ventricular loading state on right ventricular functions in one example is shown in Fig. 7. With an increase in preload and afterload in the left ventricle, right ventricular end-systolic points (left upper corner of pressure-volume loops) moved a little to the upper left. In situ, the loops would be present between loop 1 and loop 3 in this figure. Although the above small differences may be present, the essential characters observed under low COPP and hypoxia would have the same tendencies in vivo.

Effects of COPP and/or hypoxia on right ventricular ESPVR

Although pulmonary embolism is always accompanied by hypoxia, there are few reports on the effects of hypoxia on cardiac function^{6,7,8}. In our results, hypoxia of PaO_2 51 ± 2.3 mmHg under normal COPP did not decrease the slope of right ventricular ESPVR and increased coronary flow. However, if COPP declined, CS developed at a higher COPP with hypoxia, than without hypoxia. From these results, we can infer that under normal COPP, hypoxia of the above level can be compensated with an increase of coronary flow even under moderately increased afterload. If COPP declines beyond some level with hypoxia, shortness of oxygen supply to myocardium develops since vasodilation has been already induced by hypoxia. Coronary reserve, which compensates for the decrease of coronary perfusion pressure, does not remain.

A similar relationship was observed in the left ventricle with a coronary stenosis in an experiment by Coetzee et al.⁹ They examined the effects of a decrease in inspired oxygen fraction from 0.3 to 0.1 on the global and regional function of canine left ventricles, with or without stenosis of the left anterior descending coronary artery. Without stenosis, dp/dt increased, and $dp/dt/p$ and regional function did not change when the partial pressure of oxygen was decreased, while with stenosis, dp/dt and $dp/dt/p$ did not change, but regional function decreased. Coetzee explained that the reason for this is when the PaO_2 decreases, coronary arteries dilate and coronary flow increases, so the oxygen demand of heart muscle is satisfied. On the

other hand, when the PaO_2 is decreased with stenosis of the left anterior descending coronary artery, coronary flow does not increase sufficiently to satisfy the oxygen demand of the heart muscle.

Berne⁸ et al reported that the dilatation of the coronary artery in the hypoxic state was caused by the release of adenosine from ischemic tissue.

With hypoxia under normal COPP, right ventricular ESPVR shifted to the left. The potential source for this mechanism would be an increase in passive wall stiffness through coronary vessel dilation due to hypoxia.

In the present study, CS developed at COPP of 51 ± 5.1 mmHg under normal PaO_2 . Urabe et al¹⁰ in an experimental study with microsonometers, reported that the critical COPP of the right ventricle was 25–35 mmHg. The difference in the critical COPP between our study and Urabe's could be explained in two ways. First, Urabe et al examined only the regional function by placing microsonometers on the free wall of the right ventricle, while we examined the global function of the right ventricle. Therefore, the septal portion of the left ventricle affected the global function of the right ventricle. Second, they investigated wall function with shortening fraction of segmental length, while we investigated pressure-volume relationships. Since shortening fraction depends on preload and after load, evaluation of regional wall function based on segmental length should utilize its relation to tension. However, in the right ventricle with a complicated geometry it is difficult to measure accurately regional wall curvature essential to the calculation of muscle tension. The present balloon method on the other hand, conforms to the complicated shapes. In acute cor pulmonale with systemic hypotension, the entire right ventricular function affects its hemodynamics.

Therapy for acute cor pulmonale

When RVEDP was increased from 10 mmHg to 15 mmHg and from 20 mmHg to 25 mmHg, dp/dt/p decreased significantly although stroke volume increased. However, when RVEDP was increased to more than 25 mmHg, stroke volume did not increase any more. The fact that both dp/dt/p and slope in ESPVR declined with an increase in preload suggests that with a decrease in COPP, elevation of right ventricular diastolic pressure begins to aggravate myocardial blood flow at its lower pressure. When systemic vas-

cular resistance was increased to elevate COPP, right ventricular stroke volume increased significantly, but dp/dt/p did not change. When dobutamine was administered, both stroke volume and dp/dt/p increased significantly. We used a large amount of dobutamine because once the contractility decreased, cardiac output and COPP decreased, causing a further decrease in contractility. Thus a vicious circle began, which finally resulted in ventricular fibrillation. Therefore, we had to restore contractility rapidly.

The present results imply that increasing systemic vascular resistance and/or dobutamine administration are effective for acute cor pulmonale in critical state, whereas increasing RVEDP is not. Dopamine, which increases both contractility and systemic vascular resistance in further doses, may be a candidate for this purpose. However, Jordin et al¹³ reported that despite the improved cardiac index resulting from inotropic drug infusion, there was an increase in arterial hypoxemia in patients with massive pulmonary embolism and circulatory failure. The reason for this may be that increased pulmonary blood flow occurs where VA/Q is low and the shunt ratio increases. Thus, dobutamine administration improves cardiac function but may decrease PaO_2 .

Summary and clinical implication

In pulmonary embolism, the process to cardiac deterioration is more complicated since not only hemodynamics but also humoral factors (e.g. serotonin, prostaglandin^{14,15,16}), coagulant factors¹⁷ and neutral factors are operative. In our study without hypoxia, critical state developed at a COPP of 51 ± 5.1 mmHg and with hypoxia it developed at significantly higher COPP than without hypoxia.

In cases of pulmonary embolism with coronary stenosis, the critical coronary perfusion pressure may become higher, so that a slight decrease in blood pressure may lead to a decrease in cardiac contractility. In addition to a basic and principal treatment to decrease afterload, we suggest increasing PaO_2 by administering oxygen, increasing COPP with an alpha-stimulant, intra-aortic balloon pumping, and administration of a betastimulant would be optimal hemodynamic therapy for acute cor pulmonale in critical state.

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