PATHOPHYSIOLOGY IN PULMONARY HEART DISEASES,
WITH SPECIAL REFERENCE TO ROLE OF
PULMONARY HYPERTENSION, HYPOXEMIA AND
RIGHT VENTRICULAR HYPERTROPHY ON
RIGHT HEART FAILURE*

TATSUO SATAKE, KAZUO RYUGE, AND TAKEO IIDA

Promotive factors to lower seriously the mean tissue oxygen tension of the right ventricle were mathematically calculated by means of digital computer, considering that congestive cardiac failure in pulmonary heart diseases was caused by the oxygen deficiency in the right ventricular muscles. One of factors would be pulmonary hypertension related to alveolar hypoxia or asphyxia caused by disturbances of pulmonary gas exchange, and the other would be relative coronary insufficiency due to increase in works of the right ventricle caused by pulmonary arterial hypertension and decrease in coronary blood flow. Also, the results suggested that right ventricular hypertrophy itself predisposed relatively little to congestive cardiac failure.

Therefore, in most cases without complications such as mechanical disturbances of coronary vessels, arteriosclerosis, and so forth, could pulmonary infections be protected, clearing of airways be maintained and arterial gas compositions would remain within normal limits, signs of congestive cardiac failure would not appear even if there existed much impairments of tissues in the lungs.

PULMONARY arterial pressure measured by many previous workers seemed to be a function of arterial oxygen tension in the normal residents living at various high altitudes. When alveolar and arterial oxygen tension was reduced increasing altitude, the mean pulmonary arterial pressure was inversely increased. This was not only observed in the normal residents living at altitudes,¹⁻⁸ but also observed in the sea level patients whose arterial oxygen tension was re-

markably decreased by chronic obstructive lung diseases as indicated in Fig. 1.

According to *Hultgren*,⁹ the ratio of the weight of the right ventricle to that of the total heart was 30% in the subjects living at about 12,000 feet of altitude. This value was considerably higher than 21% obtained in the sea level residents, and indicates a marked right ventricular hypertrophy due only to chronic alveolar hypoxia, of course, without primary anatomical changes of lungs. Authors have been particularly interested in these physiological and anatomical changes occurred in the pulmonary circulatory system of both subjects, one of them subjected to high altitudes and the other is the patient with chronic obstructive lung disease living at sea level.

In this brief paper, authors would like to

Key Words:

Right heart failure
Alveolar hypoxia
Chronic pulmonary hypertension
Right ventricular hypertrophy
Pulmonary cripple
Increase in works of the right ventricle
Coronary blood flow

(Received for publication: April 11, 1973)

2nd Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, Japan

* This paper was presented in Symposium "Pulmonary Heart Disease" of the 5th Asian-Pacific Congress of Cardiology (1972).

Fig. 1. Mean pulmonary arterial pressure in residents correlated with altitudes (X1-X8) and in chronic obstructive lung diseases (●: chronic pulmonary emphysema, ○: bronchial asthma, ▲: chronic bronchitis, □: pulmonary fibrosis).

Fig. 2. A simplified tissue model and all necessary parameters in order to calculate the mean tissue oxygen tension of right ventricle.

represent some of the interesting results on the effects of pulmonary arterial hypertension and other factors upon the mean tissue oxygen tension of right ventricular muscles, considering that congestive cardiac failure in pulmonary heart diseases was caused by the oxygen deficiency in the right ventricular muscles. Many attempts were undertaken to measure the myocardial tissue oxygen tension directly, however, not yet sufficiently succeeded on account of many methodological limitations. Consequently, authors attempted to calculate it mathematically in the Krogh's model¹⁰ under different physiological and anatomical conditions by means of digital computer.

METHODS

Fig. 3. Myocardial tissue oxygen tension of right ventricle as determined by regional conditions.

A: oxygen consumption $\propto$ work

D: diffusion coefficient

F: blood flow

R: 1/2 intercapillary distance $\propto$ hypertrophic ratio of ventricular muscles.

The gases exchanged in the tissues might not be much dependent on the size of the cells, but be remarkably dependent on the intercapillary distance of the tissues. Authors assumed in the reference to Myers and Honig's¹¹ experimental results in the left ventricle that the half-intercapillary distance is approximately 14 micron in the right ventricle, and 18 micron in the left ventricle. These values were estimated considering that the mean transverse diameter of right ventricular muscle fibres was 10.1 ± 2.0 micron and those of the left was 13.1 ± 2.7 micron in 49 autopsy hearts of our cases,¹² but tissue length and diameter in vivo was different from in vitro, and that tissues shrinkage in the course of preparing the specimens. Now, it was assuming that if the cells between the two capillaries were swollen, the intercapillary distance must be increased proportionally with the increase of the cell volume, without any reserved vascular beds opened in hypertrophied cardiac muscles.

A simplified tissue model of the ventricular tissue as shown in Fig. 2 was invented, in order to make clear understanding of the relationship between the tissue oxygen tension and the cardiac muscle fibre hypertrophy of the right ventricle. A cylinder is shown with only one capillary through its longitudinal axis. Mean oxygen tension of this tissue cylinder could be obtained by integrating the oxygen tension between the limit of small and capital R at the L section which must be the half way between the arterial and venous end of the capillary. The final

Fig.4. Myocardial tissue oxygen tension in healthy and pulmonary heart diseases.

equation by which the mean myocardial tissue oxygen tension, shown as $\bar{P}$, is represented like Kety!¹⁰ However, with all necessary parameters, namely, equation showing the characteristics of the oxyhemoglobin dissociation curve and physiological properties of the right ventricle to a digital computer, could assume a very characteristic changes.

RESULTS

Fig. 3 represents the changes of the mean myocardial tissue oxygen tension of the right ventricle in the various parameters. The mean myocardial oxygen tension of the right ventricle in the normal condition in which all parameters are absolutely within normal physiological limits was 33 mmHg. When only the half-intercapillary distance increases by 50%, without any change in other parameters, the mean myocardial oxygen tension was decreased only by 5 mmHg as indicated by the curve R. On the contrary to this lesser change in the oxygen tension, with the increase of the mean pulmonary arterial pressure by 21 mmHg, in other words, with the increase of the total work of the right ventricle by about 50%, the mean myocardial oxygen tension was decreased by 11 mmHg as shown in the curve A. With the increase of the mean pulmonary arterial pressure by 28 mmHg, in other words, with the increase of the total work of the right ventricle by about 100%, it was strikingly decreased by 20 mmHg. On the other hand, the mean myocardial oxygen tension was increased by 10 mmHg with the increase in coronary blood flow by 50% as indicated by the curve F. On the contrary, it was decreased by 18 mmHg with the

decrease in coronary blood flow by 50%.

After knowing this type of beautiful work done by a computer, authors could show as follows; Though the arterial oxygen tension was decreased to 55 mmHg, for instance due to pulmonary cripples, hypoxemia itself lowered both the mean intercapillary oxygen tension and the mean myocardial oxygen tension by only 5 mmHg owing to the special characteristics of oxyhaemoglobin dissociation curve. On the other hand, if the pulmonary arterial pressure elevated by 100% accompanied with increase in the half-intercapillary distance by 50%, the mean myocardial oxygen tension of the right ventricle would go down from 33 mmHg to 13 mmHg supposing that the arterial oxygen tension remained within the normal range as shown in the middle of Fig.4. Of course, no increase in coronary blood flow was observed in these cases. However, these events had the serious influence upon such patients. Because, the rapid decrease in their alveolar oxygen tension under the ventilatory impairments resulted a marked increase in pulmonary arterial pressure and work of the right ventricle!¹³ If these conditions are prolonged and coronary blood flow could not increase more than 50%, the mean myocardial oxygen tension in the right ventricular muscles should be strikingly decreased as shown in the right of Fig.4, as far below the critical level at which fibres of the cardiac muscle must be destroyed markedly due to metabolic disturbances.

Fig. 5 and Fig. 6 show electron-microscopic findings of the right cardiac muscle fibres of experimental dogs with chronic pulmonary ar-

Fig.5. Electron-microscopic figure of the right cardiac muscle fibres of experimental chronic cor pulmonale (mean pulmonary arterial pressure 21 mmHg).

Fig.6. Electron-microscopic figure of the right cardiac muscle fibres of experimental chronic cor pulmonale (mean pulmonary arterial pressure 28 mmHg).

terial hypertension. Destroyed cardiac muscle fibres with marked hypertrophy, extended diameter and no increase in capillary beds are shown.

DISCUSSION

Myers *et al.*¹¹ reported the number of capillaries in the left ventricular muscle as 750~1100/mm² and the mean half-intercapillary distance as 16.5~20.5 microns by means of isotope in healthy dogs breathing quietly. Mean-while, it was reported that the cardiac muscle fibres and capillaries were distributed in one to one correspondence, and the number of capillaries was accounted as 5,000/mm² in autopsied heart.¹⁴

These discrepancies represent so called reserved vascular beds. The reserved vascular beds are closed in ordinary conditions, but opened in acute exacerbation to overload the heart with increase in blood flow.

Therefore, oxygen pressures in cardiac muscle fibres could be kept to be normal. However, it could be interpreted from our electron-microscopic findings that both cardiac muscle fibres and capillaries were destroyed in the hypertrophied heart, so in acute exacerbation in the overloaded heart, none or less of reserved vascular beds could be opened. Therefore, authors consider those assumptions to be reason-

TABLE I THE INCIDENCE OF CONGESTIVE CARDIAC FAILURE AT THE RESPECTIVE DEGREE OF PULMONARY FUNCTIONS IN 127 PATIENTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASES

<i>respiratory function</i>	<i>degree</i>	<i>number of cases</i>	<i>incidence of congestive heart failure</i>
% VC	over 76%	87	4.6%
	below 75%	40	20.0%
	below 55%	15	40.0%
FEV ₁ %	over 56%	57	0.0%
	below 55%	70	17.1%
	below 40%	36	22.2%
% MVV	over 41%	71	4.2%
	below 40%	56	14.7%
	below 30%	39	21.5%
Pao ₂	over 71 mmHg	40	0.0%
	below 70 mmHg	45	21.1%
	below 55 mmHg	13	69.2%
Paco ₂	below 49 mmHg	61	3.3%
	over 50 mmHg	24	41.7%
	over 60 mmHg	3	100.0%

able.

Now, according to our preliminary report,¹⁵ the appearance of congestive cardiac failure in the patients with chronic obstructive lung diseases seemed to be related to respiratory functions, especially to changes in arterial blood gases which were affected by the disturbances of the pulmonary gas exchange. Of course, the congestive cardiac failure disappeared as arterial blood gases tended to return to normal values. Table I shows the incidence of congestive cardiac failure at the respective degree of respiratory functions in 127 patients with chronic obstructive lung diseases. Generally, it seems that arterial oxygen tensions below 55 mmHg and carbon dioxide tension above 50 mmHg tend to predispose to congestive cardiac failure. Furthermore, some abnormal electrocardiograms were observed in 38 patients and 47% of them had ST-T changes as shown in Table II. These findings were considered as the relative coronary insufficiency caused by the discrepancy of oxygen demand and supply in the heart.¹⁶ These abnormal electrocardiographic findings including right axis deviation and right ventricular hypertrophy were often observed in the patients with lower arterial

TABLE II ABNORMAL FINDINGS IN E.C.G. OF 38 CASES, CONTAINING 12 CASES WITH EPISODES OF CONGESTIVE CARDIAC FAILURE IN 127 PATIENTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASES

<i>ECG findings</i>	
<i>Axis deviation</i>	
RAD	18.4%
LAD	7.9%
<i>ST-T abnormality</i>	
at rest	47.4%
on exercise	26.3%
<i>P-Pulmonale only</i>	21.1%
<i>Right bundle branch block</i>	
incomplete	10.5%
complete	2.6%
<i>RVH</i>	
suggestive	7.9%
definite	18.4%
<i>LVH</i>	
suggestive	13.2%
definite	5.3%
<i>abnormal cardiac rhythm</i>	
sinus tachycardia	5.3%
auricular fibrillation	2.6%
premature beat	21.1%
<i>other abnormality</i>	5.3%

TABLE III REVERSIBILITY OF ARTERIAL BLOOD GASES AND A ABNORMAL E.C.G. FINDINGS AFTER PROLONGED AIRWAY CLEARINGS IN THE PATIENTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASES.

	Name	Age	Sex	before treatment				after treatment					
				Pao ₂		ECG	ST-T	Paco ₂		ECG	ST-T		
				mmHg	mmHg			mmHg	mmHg			Axis	Axis
1	J.N.	64	M	40	78	+121°	R (+)	RVH	75	58	+60°	M (-)	
22	S.T.	28	M	41	66	+115°	R (+)	RVH	102	38	+90°	M (-)	
3	T.O.	62	M	41	62	+ 80°	R (+)	LVH	68	67	+70°	R (+)	LVH
4	T.S.	62	M	46	52	+ 73°	R (+)	LVH	45	61	+53°	R (+)	LVH
5	H.Y.	31	M	50	58	+ 96°	R (+)	RVH	73	47	+99°	M (-)	RVH
6	S.M.	68	M	59	62	+ 70°	M (+)		79	43	+70°	R (+)	
7	N.K.	32	M	59	48	+ 90°	M (±)		85	45	+83°	M (-)	
8	S.N.	68	M	64	53	+ 75°	M (-)		84	41	+77°	M (-)	
9	S.A.	68	M	65	52	+ 81°	M (-)		92	42	+77°	M (-)	
10	H.Y.	42	M	65	45	+ 82°	R (+)		80	40	+82°	M (±)	
11	M.N.	43	M	64	46	+ 82°	M (-)		64	52	+78°	M (-)	
12	S.N.	62	M	82	40	+ 87°	M (±)		83	40	+86°	M (±)	
13	Y.T.	58	M	71	49	+ 76°	M (-)		86	34	+80°	M (-)	
14	K.K.	50	M	82	48	+ 69°	M (±)		67	49	+74°	M (±)	
15	A.T.	39	M	71	42	+ 80°	M (-)		84	36	+80°	M (-)	
16	S.S.	46	F	71	46	+ 79°	M (±)	LVH	78	59	+77°	M (-)	LVH
17	S.M.	70	M	75	48	+ 70°	M (+)		79	48	+70°	R (+)	
18	U.U.	53	F	50	57	- 63°	R (+)	RVH	75	43	-35°	M (-)	
19	A.Y.	65	M	59	47	+ 79°	R (+)	RVH	70	47	+81°	R (+)	RVH
20	U.O.	58	M	76	44	+ 73°	M (±)	LVH	81	32	+74°	M (-)	
21	B.T.	62	M	78	38	+ 82°	M (-)		65	46	+60°	M (-)	

R: at rest (ST-T abnormality)
M: on exercise (ST abnormality)

TABLE IV PRINCIPLE CAUSES OF DEATH AND ANATOMICAL CHANGES OF HEART IN 9 CASES WITH PULMONARY HEART DISEASE (CHRONIC COR PULMONALE)

		basic disease	immediate cause of death	total heart weight (T) g	weight of right ventricle (R) g	$\frac{R}{T}$ %	wall thickness of right ventricle mm	increase ratio of D %
1)	37 ♂	chronic pulmonary emphysema pleural adhesion	pneumonia	440	110	25	10	107
2)	40 ♂	tuberculosis	bronchitis	222	77	35	4	81
3)	42 ♂	tuberculosis	bronchitis	172	52	30	4	6
4)	49 ♀	cancer of the r- hilum, pleuritis	respiratory failure	270	42	15	5	20
5)	62 ♂	tuberculosis	respiratory failure	300	72	24	6	31
6)	64 ♂	chronic pulmonary emphysema	pneumonitis infarction	270	65	24	5	56
7)	65 ♂	tuberculosis	pneumonia	350	88	25	5	9
8)	70 ♂	chronic pulmonary emphysema	infarction	370	65	18	6	53
9)	77 ♂	chronic pulmonary emphysema	pneumonia	285	54	19	6	-3
				298 ± 79	69 ± 22	24 ± 6	5.7 ± 1.7	40 ± 37

D: mean transverse diameter of right ventricular muscle fibres

oxygen tension below 55 mHg. However, most cases showed improvement of electrocardiographic findings as hypoxemia was improved as shown in Table III. Needless to say, there was inverse correlation between the arterial oxygen tension and the pulmonary arterial pressure. Hypoxemia and right ventricular hypertrophy were frequently observed not only in the residents at high altitudes but also in the residents at sea level with chronic obstructive lung diseases. However, these factors might participate relatively little in causing a reduction of myo-

cardial tissue oxygen tension. The increase in the work of the right ventricle caused by the pulmonary hypertension due to chronic and acute alveolar hypoxia under the restrictive ventilatory impairment might participate mainly in causing reduction of myocardial tissue oxygen tension. Actually, authors could not find typical hypertrophy of the right ventricle in patients died by congestive cardiac failure in pulmonary heart diseases, except only one case which had the increase in the radius of muscle fibre by 107% as shown in Table IV. In such cases

Fig. 7. Changes of mean pulmonary arterial pressure due to an attack of coughing in bronchial asthma.

Fig. 8. Myocardial tissue oxygen tension of left ventricle as determined by regional conditions.
A: oxygen consumption $\propto$ work
D: diffusion coefficient
F: blood flow
R: $1/2$ intercapillary distance $\propto$ hypertrophic ratio of ventricular muscles.

without typical right ventricular hypertrophy, the real cause of the death might be interpreted by the acute marked decrease of the myocardial tissue oxygen tension induced by a transient marked increase in pulmonary arterial pressure due to pulmonary cripple, especially in the cases with both prolonged chronic pulmonary hypertension and right ventricular hypertrophy.

Because, following two reasons could be mentioned in such cases, First; In spite of low oxygenation in right ventricular muscles caused by marked pulmonary arterial hypertension, circulatory adaptations such as opening of reserved

vascular beds as described, could not be maintained due to cardiac muscle hypertrophy and destruction. Moreover, it was well known that the coronary blood flow decreased due to remarkable dilatation of right ventricle caused by acute pulmonary arterial hypertension. Second; In chronic low oxygenated cardiac muscles, enzymes such as cytochrome oxidase, succinate oxidase, DPNH oxidase and dehydrogenase, increased as much as 30% or more to accelerate anaerobic metabolism.¹⁷ These cellular acclimatization could be observed in chronic phase, however in acute phase of remarkable pulmonary hypertension, less time was available for these excellent acclimatization.

Of course, these results would indicate that any factor which causes a striking rise in the pulmonary arterial pressure predispose to failure of the heart. There are many factors to be taken into consideration at this point, however among them all authors think it is worth pointing out the unfavorable effect of cough. Fig. 7 shows the mean pulmonary arterial pressure changes of one subject with bronchial asthma, who coughed continuously during right heart catheterization. It can be seen that an attack of coughing cause a marked rise in the pulmonary arterial pressure from 17 mmHg to above 50 mmHg. Although authors¹⁸ happened to know the extent of the effect of cough on pulmonary arterial pressure, this is due to the continuous elevation of intraalveolar pressure which is caused by check valve mechanism of lung airways. That is, cough could also become a cause of death in the natural history of pulmonary heart diseases because the pulmonary arterial pressure would be elevated remarkable in that instance.

On the other hand, it should be considered sufficiently that hypercapnia would not only increase pulmonary arterial pressure but also decrease cardiac output and predispose to congestive cardiac failure, as authors¹⁹ had presented another papers which was studied in experimental dogs under isoventilation using body respirator.

Finally, authors would like to present that in the case of the left ventricle, in order to compare the difference between the right ventricle and the left ventricle, the very decline to the proportion of the increase in R and A were shown as Fig. 8. This result shows that in the same condition the left ventricle is more easily apt to fall into congestive cardiac failure than the right ventricle.

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