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Chapter 9
Time-Course of Ventilation, Arterial and Pulmonary CO_2 Tension During CO_2 Increase in Humans

Toru Satoh, Yasumasa Okada, Yasushi Hara, Fumio Sakamaki, Shingo Kyotani, Takeshi Tomita, Noritoshi Nagaya, and Norifumi Nakanishi

Abstract A change of ventilation (VE), $PaCO_2$ (arterial CO_2 tension) and $PvCO_2$ (pulmonary arterial CO_2 tension) with time was not evaluated precisely during exercise or CO_2 rebreathing in humans. In this study, changes of these variables with time were fitted to exponential curves {y=Exp (x/ T+A)+k} and compared. When exercise pulmonary hemodynamics was examined in 15 cardiac patients to decide therapies, we asked the patients to undergo CO_2 rebreathing using air with supplementation of consumed O_2. Arterial and pulmonary blood was drawn every minute. During exercise, T was 28.2±8.4 and 26.8±12.4, and A was 0.80±0.50 and 0.50±0.90 in VE and $PvCO_2$, respectively, with no statistical differences. During CO_2 rebreathing, T was 18.6±5.8, 41.8±38.0 and 21.6±9.7 and A was 0.39±0.67, 1.64± 1.35 and 0.17±0.83 in VE, $PaCO_2$ and $PvCO_2$, respectively, with statistical difference of $PaCO_2$ from other variables, suggesting that VE and $PvCO_2$ showed same mode of change according to time but $PaCO_2$ did not.

Keywords Ventilation • $PaCO_2$ • $PvCO_2$ • CO_2 rebreathing

9.1 Introduction

A change of VE, $PaCO_2$ and $PvCO_2$ with time was not evaluated precisely during CO_2 increasing state like exercise or CO_2 rebreathing in humans. Gelfand and Lambertsen (1973) studied time course of ventilatory change by abruptly adding and removing CO_2 in inhaled air and reported that there were three respiratory components with differing onset lag time and time constant. We did a similar analysis of $PaCO_2$ and $PvCO_2$ as well as VE during CO_2 rebreathing and exercise tests in 15 cardiac patients. We performed exercise test with arterial and pulmonary arterial blood sampling to make therapeutic

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C.A. Nurse et al. (eds.), *Arterial Chemoreception: From Molecules to Systems*,
Advances in Experimental Medicine and Biology 758, DOI 10.1007/978-94-007-4584-1_9,

decisions for cardiac patients. Then we asked them to undergo CO_2 rebreathing test after explanation of the study purpose to elucidate CO_2 and ventilatory kinetics and know ventilatory control mechanics. We fitted the plotting of $PaCO_2$, $PvCO_2$ and VE with time, to exponential curve. Time constant and fixed constant values of the resultant equations in each variable were calculated and compared each other to see the relation of $PaCO_2$, $PvCO_2$ and ventilation.

The results suggest that the fitted equation of VE with time was statistically different from the fitted equation of $PaCO_2$ with time, but not from the fitted equation of $PvCO_2$ with time. Implication of our results is that VE and $PvCO_2$ are changed identically, but it must await further study that this relation is a cause or a result. We report this result because it may add new insights to ventilation research in terms of CO_2 kinetics.

9.2 Methods

9.2.1 Study subjects

The study subjects were 15 patients with cardiac disease, who underwent pulmonary hemodynamic investigations in order to help determine their treatment plans. Eleven had mitral valvular heart disease (4 dominant mitral stenosis, 4 dominant mitral regurgitation and 3 combined mitral stenosis and regurgitation), 2 had dilated cardiomyopathy, and 2 had chronic pulmonary thromboembolism. No patient had ventilatory disorder. Their age was 51 ± 15 years (mean$\pm$S.D.). Eight patients were male and seven were female. The purpose, protocol and risks of the present study were fully explained, and written informed consent was obtained from each patient.

9.2.2 Protocol

The patients performed exercise on an upright cycle ergometer 4 h after their usual breakfast and medication, with a Swan-Ganz catheter inserted via the right internal jugular vein into the pulmonary artery and a fine arterial catheter inserted via the left radial artery. They pedaled at a speed of 55 rpm without any added load for 1 min. Then the load was increased by 1 W/ 4 s (15 W/ min) to the symptom-limited maximum. Continuous hemodynamic monitoring, including that of arterial and pulmonary arterial pressures, and expired gas analysis (AE280, Minato Medical Instruments, Osaka) were performed every 6 s throughout the period of exercise. Expired ventilation (VE) was measured by hot-wire flowmeter. Arterial and pulmonary arterial blood samples were collected before exercise and every minute during exercise for blood gas analysis. On the same day, 3 h after lunch, the subjects were tested during CO_2 rebreathing using a bag containing 6 l of air, with the same hemodynamic, expired gas and blood gas analyses as during exercise. Oxygen consumption (VO_2) was determined in advance and an equal amount of O_2 was supplemented into the rebreathing bag to maintain a constant inspired O_2 concentration throughout the rebreathing test.

9.2.3 Fitting to Exponential Curve

VE, $PaCO_2$ and $PvCO_2$ were plotted against time. As the relations resembled exponential curve, they were fitted to $y = \mathrm{Exp}(x / T + A) + k$. Figure 9.1 demonstrated a representative case during CO_2 rebreathing.

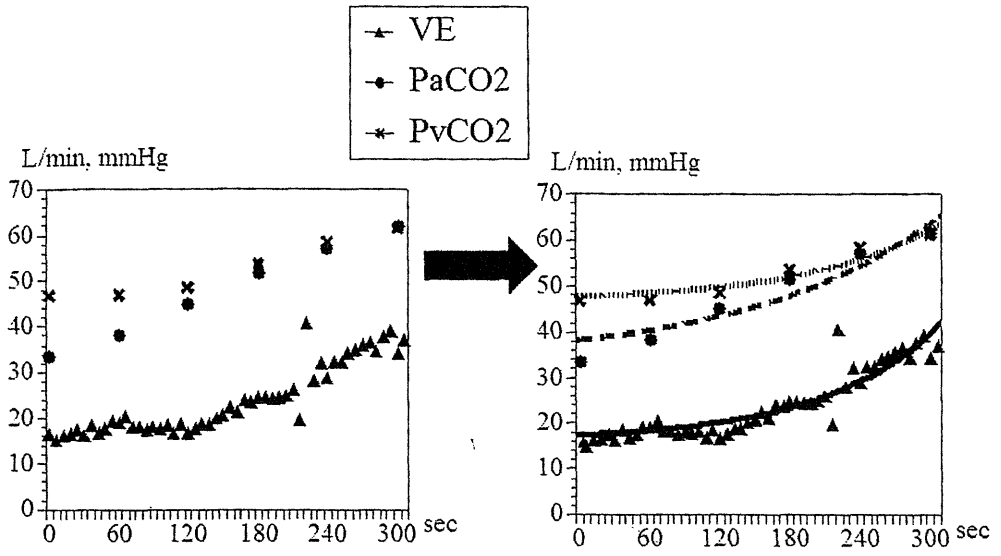

Fig. 9.1 Representative example of fitting to exponential curve. VE, $PaCO_2$ and $PvCO_2$ were determined by averaging forward and backward 5 values. In this example, VE was fitted to $y=EXP(x/16.6+0.079)+16.4(R^2=0.87)$, $PaCO_2$ to $y=Exp(x/27.5+1.56)+33.5(R^2=0.92)$ and $PvCO_2$ to $y=Exp\ (x/19.3+0.114)+46.8(R^2=0.93)$

VE was determined by averaging forward and backward 5 values. In this example, VE was fitted to $y=Exp\ (x\ /\ 16.6+0.079)+16.4\ (R^2=0.87)$, $PaCO_2$ to $y=Exp\ (x\ /\ 27.5+1.56)+33.5\ (R^2=0.92)$ and $PvCO_2$ to $y=Exp\ (x\ /\ 19.3+0.114)+46,8\ (R^2=0.93)$.

9.2.4 Analysis

T and A were calculated in 15 patients both during exercise and CO_2 rebreathing. T as well as A in VE, $PaCO_2$ and $PvCO_2$ were compared to each other during exercise and CO_2 rebreathing.

9.2.5 Statistics

Fitting was carried out by Deltagraph Pro 5.5.1 (SPSS Inc. and Red Rock Software Inc. USA). Comparison of T as well as A in VE, $PaCO_2$ and $PvCO_2$ were done by student-*t* test. Values of $p<0.05$ were considered significant.

9.3 Results

9.3.1 Changes in Pulmonary Hemodynamics

VO_2, PaO_2 and arterial pH during exercise are shown in Table 9.1. PaO_2 did not change significantly, as in healthy subjects. Arterial pH was only slightly lowered. Figure 9.2 depicts changes in $PaCO_2$, $PvCO_2$ and VE at rest, and at the RC point in exercise or at the maximal response in CO_2 rebreathing. $PaCO_2$ did not change during exercise (38.3±3.7 to 39.5±5.4 mmHg), but was markedly elevated

Table 9.1 Patient characteristics during exercise

	Rest	RC point	Peak exercise	Statistics
MPA (mmHg)	21 ± 9	50 ± 17		
PCW (mmHg)	12 ± 6	31 ± 12		
VO_2 (ml/min/kg)			18.3 ± 4	
PaO_2 (mmHg)	112 ± 17	107 ± 22		ns
PH	7.37 ± 0.03	7.34 ± 0.05		p=0.02

RC point: respiratory compensation point, when end-tidal CO_2 concentration begins to decrease. Ventilation is linearly related to CO_2 excretion until the RC point. PaO_2: arterial O_2 partial pressure; mPA: mean pulmonary arterial pressure; PCW: pulmonary capillary wedge pressure; VO_2: oxygen consumption; pH: arterial blood pH; ns: not significant; PaO_2 and pH at rest are compared with those at peak exercise by paired *t*-test

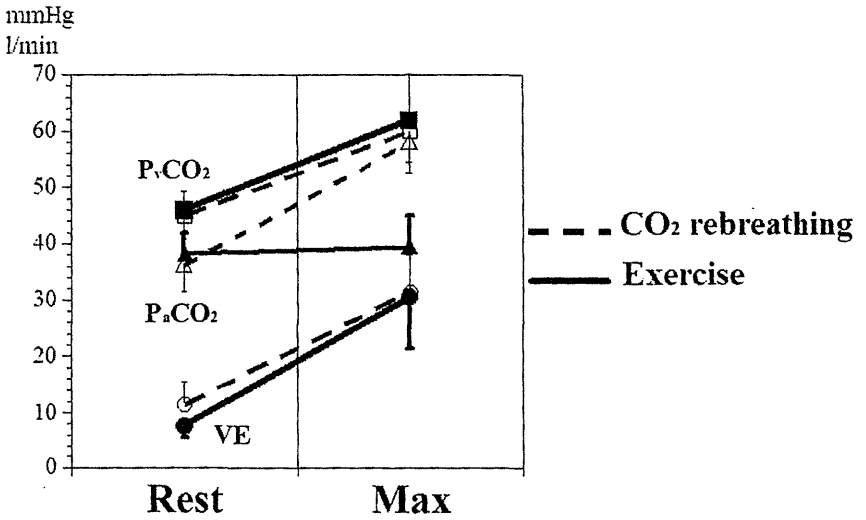

Fig. 9.2 Mean changes in VE, $PaCO_2$ and $PvCO_2$ during exercises and CO_2- breathing for 15 patients. Changes during exercise are shown as *solid lines*. Changes during CO_2 rebreathing are shown as *broken lines*. $PaCO_2$, $PvCO_2$ and VE before both examinations are shown as at rest. Three variables at the RC point in exercise and at the maximal response in CO_2 rebreathing are shown as at Max. See text for details. $PaCO_2$: arterial CO_2 partial pressure; $PvCO_2$: mixed venous CO_2 partial pressure; VE: Ventilation

during CO_2 rebreathing (36.3±4.9 to 58.0±5.5 mmHg). $PvCO_2$ increased greatly during both exercise (45.6±3.3 to 61.9±8.2 mmHg) and CO_2 rebreathing (45.3±4.2 to 60.2±5.5 mmHg). VE increased from 7.5±2.2 to 30.5±9.1 l/min during exercise and from 11.5±4.0 to 31.4±6.7 l/min during CO_2 rebreathing.

9.3.2 T and A

T and A in the fitting equation during exercise and CO_2 rebreathing are shown in Tables 9.2 (CO_2 rebreathing) and 9.3 (Exercise). Fitting of 3 variables in all subjects was appropriate because second power of fitness of fitting equations were more than 0.8.

Mean values of T as well as A for VE, $PaCO_2$ and $PvCO_2$ during CO_2 rebreathing are depicted in Fig. 9.3. A and T for $PaCO_2$ were statistically different from A and T for VE and $PvCO_2$.

Mean values of T as well as A for VE and $PvCO_2$ during exercise are depicted in Fig. 9.4. Neither was not statistically different during exercise.

Table 9.2 A and T of fitting equations in each variable during CO_2 rebreathing

	A			T		–: not measured
Patient	VE	$PaCO_2$	$PvCO_2$	VE	$PaCO_2$	$PvCO_2$
1	1.52	1.4	1.56	30.6	34	48.1
2	0.29	2.8	–0.85	16.9	48.5	14.1
3	0.64	2.32	0.2	11.7	36.2	10.3
4	–0.26	2.8	0.86	14.1	52.9	23.8
5	0.96	2.18	–1.35	17.6	25.5	10.2
6	0.99	2.59	–0.54	22.9	52.9	17.5
7	–0.72	1.39	0.15	11.6	27.8	19.9
8	0.22	0.41	0.61	24.1	17	20.5
9	1.5	2.2	1.1	27	44	30
10	–0.06	0.47	–0.03	19.4	17.7	21
11	–0.08	–	1.2	17.1	–	29.4
12	–0.1	–0.3	–0.3	10.7	11.7	14.2
13	0.47	3.8	0.07	20	159	23.5
14	0.02	–0.79	–0.36	16.6	16.5	19.9
15	0.33	1.83	0.02	17.7	40.0	22.5

Table 9.3 A and T of fitting equations in each variable during exercise

	A		T	
Patient	VE	$PvCO_2$	VE	$PvCO_2$
1	0.58	0.39	26.1	23.6
2	0.42	0.76	26	29
3	1.5	–0.03	33.4	24.4
4	1.34	1.3	44.4	56.6
5	1.6	0.94	36.9	32.8
6	1.1	0.25	18.2	16.8
7	0.53	–0.79	22.9	16.6
8	–0.58	–2	15.4	11.9
9	0.49	0.89	38.3	42.4
10	0.8	–0.3	17.6	10.8
11	0.86	0.94	29.7	30.5
12	0.59	0.7	30.2	25.5
13	1.2	0.27	26.1	20
14	0.41	1.37	22.2	35.7
15	1.1	0.7	35.5	34.5

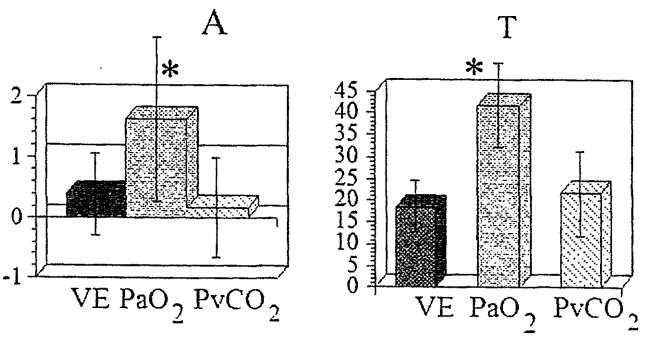

Fig. 9.3 Mean values of A and T in VE, $PaCO_2$ and $PvCO_2$ during CO_2 rebreathing. Mean values of T as well as A in VE, $PaCO_2$ and $PvCO_2$ during CO_2 rebreathing were depicted. A and T in $PaCO_2$ were statistically different from A and T in VE and $PaCO_2$

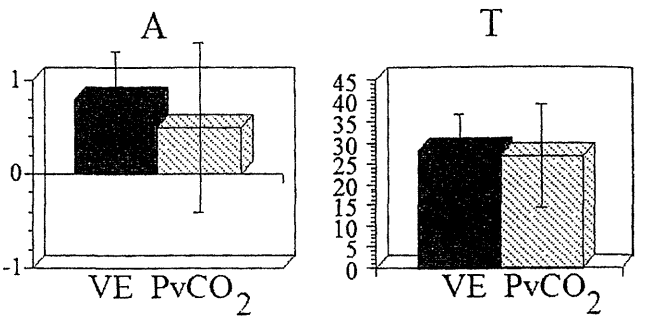

Fig. 9.4 Mean values of A and T in VE and $PvCO_2$ during exercise. Mean values of T as well as A in VE and $PvCO_2$ during exercise were depicted. Both were not statistically different during exercise

9.4 Discussion

This is the first report to analyze changes in VE, $PaCO_2$ and $PvCO_2$ with time and to compare those changes. VE and $PvCO_2$ showed the same mode of change but $PaCO_2$ did not.

9.4.1 Critique of Methods

We studied a diseased population and could be criticized regarding several points, if we extrapolate our results to normal healthy humans. First, patients with heart disease may have additional ventilatory stimuli such as hypoxia or acidosis during exercise. However, the cardiac patients we studied did not show a significant reduction in PaO_2, and demonstrated only a slight decrease in arterial pH. Second, the study patients might have been unique and have had some specific characteristics that led to an unusual conclusion. Among the 15 patients, four had moderate mitral regurgitation, and showed nearly normal hemodynamics during exercise. The results obtained from these four subjects may be representative of normal healthy humans. Other patients had apparently abnormal hemodynamic responses during exercise, but each of them also showed a practically equal change to time between $PvCO_2$ and VE during exercise and CO_2 rebreathing. Therefore, our results may be extended with caution to the normal healthy population, but needs to be confirmed.

Another technical problem may be that the number of sample points for $PvCO_2$ is not sufficient to fit with exponential equation time. However, most of the second power of correlation coefficients for fitting equations were more than 0.9 and at least 0.8, and the present data are considered sufficient for analysis.

9.4.2 Time Course of Respiratory Variants

We fitted the changes in ventilatory parameters (VE, $PaCO_2$ and $PvCO_2$) to exponential equations and compared the time constants and the other constants of the equations between the parameters. In their pioneering work, Gelfand and Lambertsen (1973) confirmed the existence of three different modes of ventilatory components by abruptly adding or stopping CO_2 inhalation. These three components were a peripheral chemoreceptor in the carotid body, a fast central responder to CO_2 increase and a late central responder. We obtained a different time-response equation of the respiratory variables from Gelfand's equation. This is because they inhaled stepwise increase in concentration of CO_2 gas compared to our study in which CO_2 concentration was increased little by little by rebreathing the expired air and the three components of the CO_2 response were not separated. The time constant would be changed according to inhaled CO_2 concentration, individuals, or mode of inspired CO_2 increase.

Our time constant of ventilation was about 20 s during CO_2 rebreathing, and about 30 s during exercise. Gelfand's time constant was 10 s for the fast-responding receptor and 89 s for the slow-responding one. Our time constant was obtained by adding these three components, and is considered to be a reasonable value. Our aim, however, was to compare the differences in time course of three ventilatory variables, VE, $PaCO_2$ and $PvCO_2$.

9.4.3 Close Coupling of $PvCO_2$ and VE

The strong coupling of $PvCO_2$ and VE, but not $PaCO_2$ in the pattern of change according to time, suggests two possibilities. One is that VE changes in proportion to $PaCO_2$ but another function intervenes between the two variables, leading to a different pattern of changes in VE and $PaCO_2$ according to time, and $PvCO_2$ is just the result of the VE change. Another possibility is that VE is determined $PvCO_2$, indicating $PvCO_2$ is an important stimulator of ventilation.

If $PvCO_2$ stimulates ventilation, we have to consider the existence of a venous chemoreceptor. This CO_2 chemoreceptor stimulates ventilation both during hypercapnic and eucapnic conditions (CO_2 rebreathing and exercise). Such receptors exist either in the venous system or in the pulmonary artery or pulmonary ventilatory system such as pulmonary stretch receptors (Mitchell et al. 1980; Nilsestuen et al. 1981; Green et al. 1986) or upper airway (Forster et al. 1985). Fedde et al. (1982) reported that pulmonary arterial chemoreceptors for ventilatory control exist in birds. Sheldon and Green (1982) separated the systemic and pulmonary circulation in dogs, controlled CO_2 partial pressure independently in each circuit, and measured VE. They demonstrated that respiratory output was augmented by selectively elevating pulmonary arterial CO_2 partial pressure. However, the existence of venous CO_2 chemoreceptors in mammals has not been proven. Cropp and Comroe (1961) and Sylvester et al. (1973) opposed the theory of the existence of venous CO_2 chemoreceptors in dogs, because infusion of CO_2-equilibrated blood did not initiate ventilatory responses until the infused stimulus reached the systemic arterial circulation. Orr et al. (1988) concluded that venous CO_2 chemoreceptors do not exist in the anesthetized cat, on the basis that venous CO_2 loading did not induce respiratory augmentation in the phrenic neurogram unless $PaCO_2$ was raised.

These reports support the former possibility that VE changes in proportion to $PaCO_2$ but another function intervenes between the two variables, in view of the close coupling of $PvCO_2$ and VE, but not $PaCO_2$. $PaCO_2$ does not directly change ventilation, but some other intervening sensor exists between the variables of $PaCO_2$ and VE. Further study on this issue is needed.

9.5 Summary

VE and $PvCO_2$ showed same mode of change according to time but $PaCO_2$ did not, suggesting that VE and $PvCO_2$ are changed identically with time, but further studies are required to determine whether this relation is a cause or a result. We report this result because it may add new insights to ventilation research in terms of CO_2 kinetics.

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1 診察法（身体所見のとり方）

慢性血栓塞栓性肺高血圧症（CTEPH）の診察法は，Ⅱ章の肺高血圧症の診察法と本質的には変わりはなく，これを参照して頂きたい．CTEPHにおける追加事項と肺高血圧症での補足事項を記した．

a 慢性肺血栓塞栓症でみられる心血管系の異常所見

1．肺野の血管雑音

肺高血圧症の診察所見で示した所見（「Ⅱ-1．肺高血圧症の診察法（身体所見のとり方）」表1（p28）の下線を付けた所見）以外では，肺野の血管雑音を必ず検索する．肺高血圧症でよく聴かれる三尖弁逆流による収縮期雑音と異なり，Ⅰ音からわずかの間隙があって始まり，ダイヤモンド型の駆出型の雑音を生じる．聴取する場所も心音が及ばない領域を含む．しかし，この所見が認められる頻度は決して高くなく（印象としては10%前後），感度のよい所見ではないが，特異度は高いため肺高血圧症の鑑別においては見逃さないように注意したい．

2．心臓の診察（補足）

a）頸静脈視診

①右房圧の推定：CTEPHの経過観察においても極めて有用といえる．

②波形解析：収縮期にX谷よりも外側に盛り上がるV波が観察されると，中等度以上の三尖

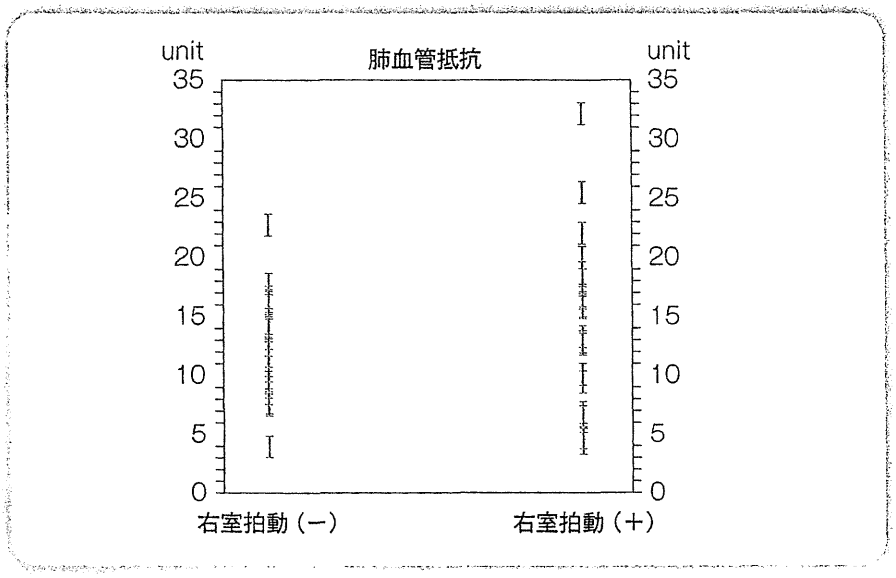

図1　右室拍動の有無と血行動態

48例中32例（66%）で右室拍動を認めた．

弁逆流が存在する．

b）右室拍動・肺動脈拍動

ある程度の肺高血圧症があってもみられないことがある．図1に示すように右室拍動の有無は肺高血圧症の重症度とは関係がなく，体格が関係しているのであろう．

c）聴診所見

Ⅱ章の肺高血圧症の聴診所見と同様のことがいえるが，特徴的な点として明瞭な肺動脈性駆出音を聴取することが多い．近位部肺動脈に狭窄があるため肺動脈開放直後に血液の駆出に抵抗があり肺動脈弁がしなって過剰音を発生するのかもしれない．以前からCTEPHではⅡ音の分裂間隔が長くなるとの報告があったが，私の経験からはほかの肺高血圧症疾患と比較して特別にこのような傾向はみられないと感じている．

d）心血管系以外の異常所見

Ⅱ章の肺高血圧症と変わった点はない．

V-10 肺高血圧症

肺高血圧症治療ガイドライン(2006年改訂版)

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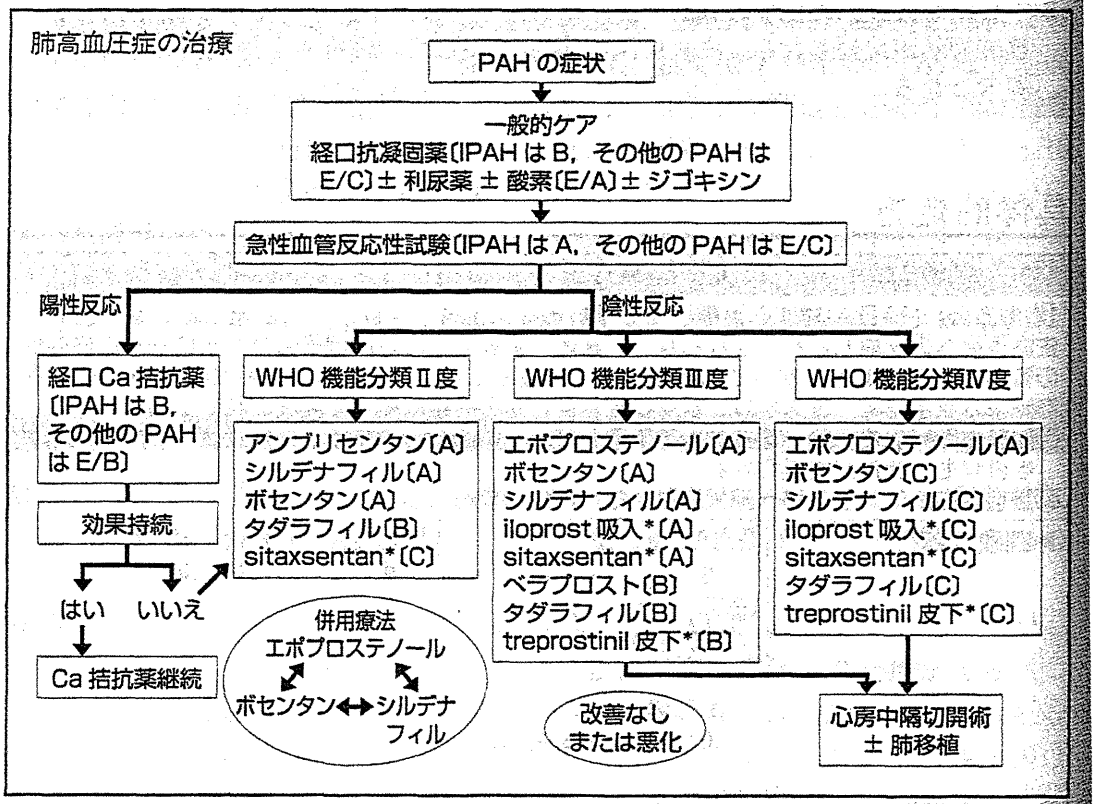
アルゴリズム



A：強く推奨，B：中程度の推奨，C：やや推奨，E：専門家の見解のみが根拠
＊：本邦未発売
(ACCP ガイドライン 2007，Eur Heart J 2009 より引用改変)

表1　IPAH／FPAH に対する治療

Class Ⅰ	・エポプロステノール	Level A
	・ボセンタン	Level A
	・肺移植	Level A
	・在宅酸素療法	Level C
Class Ⅱa	・シルデナフィル(＊)	Level A
	・抗凝固療法	Level B
	・Ca拮抗薬	Level B
	・iloprost(＊)，treprostinil(＊)，一酸化窒素(NO)(＊)	Level B
Class Ⅱb	・ベラプロスト	Level B
	・心房中隔裂開術	Level B

＊2007年7月現在，本症に対して保険未承認の薬剤
(日本循環器学会，他 編：肺高血圧症治療ガイドライン(2006年改訂版)，2006より引用改変)

IPAH：特発性肺動脈性肺高血圧症，FPAH：家族性肺動脈性肺高血圧症

総説

定義

❶肺高血圧症は表2のように分類。左心性心疾患に伴う肺高血圧症，および肺疾患／低酸素血症に伴う肺高血圧症に対しては原病の治療。慢性血栓性／塞栓性疾患による肺高血圧症に対しては，独自のガイドラインがある。本項では，肺動脈性肺高血圧症(PAH)について概説する。

❷厚生労働省および欧米のガイドラインには特発性肺動脈性肺高血圧症(IPAH)のガイドラインと記載→PAH全体に適応可能→本項ではPAHのガイドラインとする。

❸PAHの定義：平均肺動脈圧(mPA)≧25 mmHgかつ肺動脈楔入圧(PCWP)＜15 mmHgで，表2の分類2〜5を除外。20 mmHg≦PA＜25 mmHgは境界域肺動脈性肺高血圧症。

診断

❶診断基準はガイドラインに示されていない。

❷スクリーニング検査：問診，身体診察，胸部X線，心電図→可能性あり→心エコー→肺高血圧症あり→右心カテーテル検査：肺高血圧症の確定診断

表2 肺高血圧症の分類(ダナポイント分類2008)

1. 肺動脈性肺高血圧症(PAH)
   1) 特発性(IPAH)
   2) 遺伝性
   3) 薬物と毒物
   4) 各種疾患に伴う肺動脈性肺高血圧症
      ①膠原病性
      ②先天性心疾患
      ③肝臓病
      ④AIDS
      ⑤住血吸虫
      ⑥溶血性貧血
   5) 新生児遷延性肺高血圧症

1′ 肺静脈および／または肺毛細管閉塞
   肺静脈閉塞性疾患(PVOD)，肺毛細血管腫症(PCH)

2. 左心性心疾患に伴う肺高血圧症
   1) 収縮障害
   2) 拡張障害
   3) 弁膜症

3. 肺疾患および／または低酸素血症に伴う肺高血圧症
   1) 慢性閉塞性肺疾患
   2) 間質性肺疾患
   3) 混合性障害
   4) 睡眠呼吸障害
   5) 肺胞低換気障害
   6) 高所への慢性曝露
   7) 発育障害

4. 慢性血栓性および／または塞栓性疾患による肺高血圧症

5. その他の肺高血圧症
   1) 血液疾患：骨髄増殖性疾患，脾摘出
   2) 全身疾患：サルコイドーシス，ヒスチオサイトーシスX，リンパ管腫症，神経鞘腫，血管炎
   3) 代謝疾患：甲状腺疾患，糖原病，ゴーシェ病
   4) その他：肺血管の圧迫(リンパ節腫脹，腫瘍，線維性縦隔炎)

(第4回肺高血圧症世界シンポジウム，Danapoint, USA, 2008)

(図1)。

❸肺高血圧症の類似疾患(表2の分類2〜5)の除外診断。

①左心性心疾患：心エコー，②肺疾患：肺機能検査・CT，③慢性肺血栓塞栓症：肺血流シンチ，肺動脈造影。

❹PAHの中での鑑別

①IPAH：他疾患を除外するほか，*BMPR2*などの遺伝子異常の検索も有用(30〜40%で発現し，陽性的中率は高い)。

②膠原病性：自己抗体検査。

③先天性心疾患：コントラスト心エコー検査により右左シャントを確認。

④肝疾患：肝機能検査，腹部エコー。

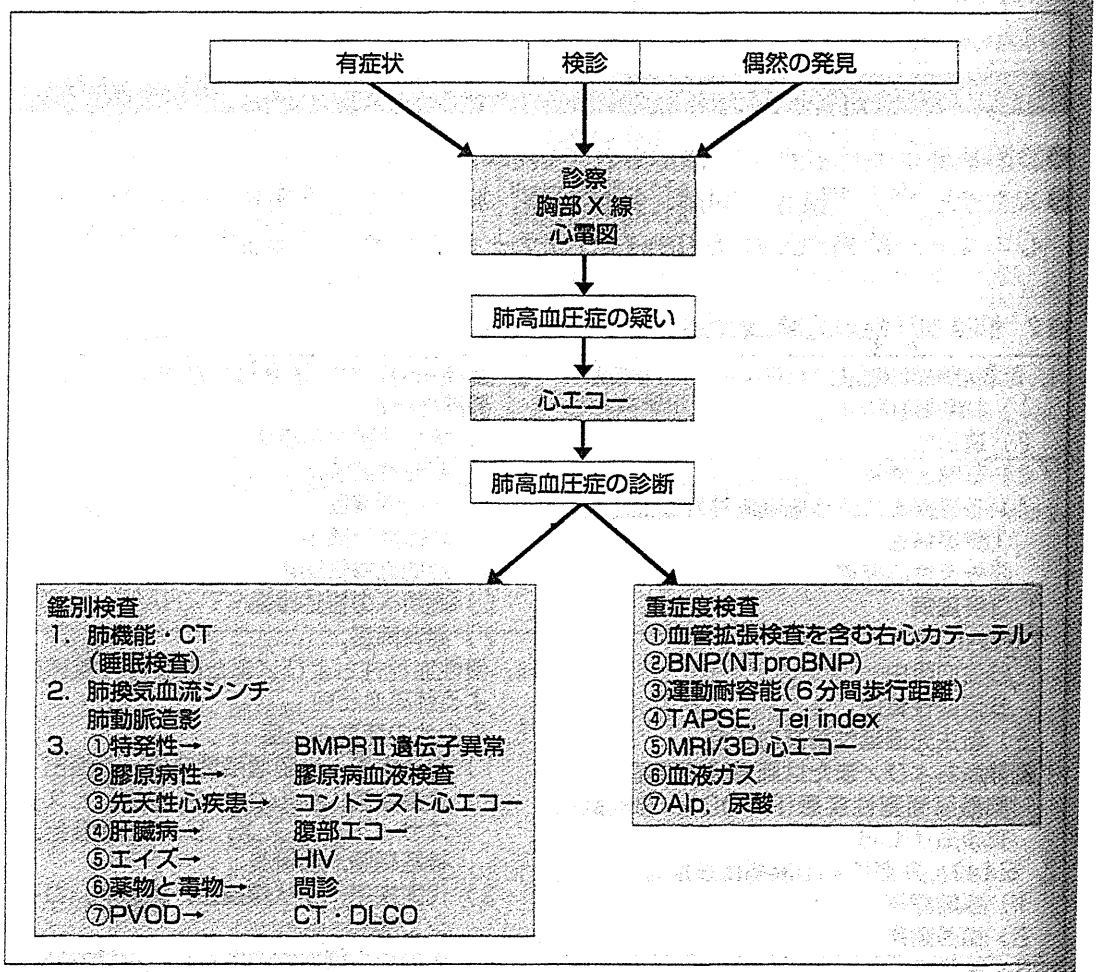


図1

(Barst RJ：J Am Coll Cardiol 43：40S-47S, 2004より引用改変)

治療方針

❶右心カテーテル検査時の急性血管反応性試験
①血管拡張薬(NO 吸入，100%O_2 吸入，アデノシン静注，ニソルジピン点滴静注，エポプロステノール点滴静注など)により肺動脈圧低下度の測定。
②陽性(mPA が 10 mmHg 以上低下し 40 mmHg 以下となる)：Ca 拮抗薬を血圧が許容する限り増量。
③陰性：新しい血管拡張薬(アルゴリズム，表 1)を投与。投与順序はガイドライン上では明確でない。
❷WHOⅣではエポプロステノールのみ推奨度が高い。→重症例にはエポプロステノール。
❸併用療法：以上の治療で反応の乏しい症例には血管拡張薬を併用。
❹併用療法でも治療に対する反応が不良な症例では肺移植。両肺移植，生体移植が行われる。

◆治療方法
❶一般的治療：表 3「従来の治療」に示す。
❷新しい治療
①急性血管反応性試験陽性例：上述を参照。陽性例は日本では非常に少ない。
②急性血管反応性試験陰性例
1) WHOⅡ，Ⅲ：エンドセリン受容体拮抗薬(ボセンタン，アンブリセンタン)，PDE-Ⅴ阻害薬(シルデナフィル，タダラフィル)を単独あるいは併用。場合によりエポプロステノールを投与。
2) WHOⅣ：ヒックマンカテーテルを留置し，エポプロステノールを在宅静注。比較的急速に増量する(4 日～1 週間に 1 度，1 ng/mL/分ずつ増量)。

表 3 肺高血圧症の治療

従来の治療	1. 生活様式 運動量の制限，女性の妊娠の禁止
	2. 右心不全 ジゴキシン 利尿薬(フロセミド，スピロノラクトン)
	3. 低酸素血症—酸素吸入
	4. 抗凝固薬—ワルファリン
	5. 血管拡張薬 1) Ca 拮抗薬大量療法(5%に有効)
新しい治療	2) プロスタグランジン製剤 3) エンドセリン受容体拮抗薬 4) PDE-Ⅴ阻害薬
	6. 移植—5 年生存率 50% 生体・両肺・心肺・片肺移植
これからの治療	7. 血管増殖抑制剤(イマチニブ)

表4　エポプロステノール治療での留意点

1）皮下トンネル感染
2）エポプロステノールの副作用
　①血管拡張(頭痛，紅潮，下痢)
　②骨痛(下顎，足底)
　③血小板減少
3）カテーテル抜去
4）心不全の悪化
5）手技の習得

合併症・副作用については表4を参照。

3）WHOⅠ：WHOⅡと同様の内服薬での治療を開始(肺高血圧症世界会議の推奨による)。

◆エポプロステノール投与の注意点

❶エポプロステノールの適応WHOⅣでの開始は絶対適応。実際にはWHOⅡでの開始では予後が決して良くない→WHOⅢでも右心不全を認めるか，または右心不全を起こす可能性が高い状態で開始。

❷エポプロステノール使用の注意点

①留置カテーテルの使用(合併症もあり)→なるべく開始は遅らせる。

②WHOⅣでの開始では予後不良→WHOⅢでi)心不全あり　ii)心不全の既往あり　iii)心不全を早晩起こす肺循環動態では開始すべき

③開始時期が遅れると予後不良←エポプロステノール単独で治療された時代より，各種内服治療薬が出現してからの方が予後は悪化している。

④エポプロステノールによる右心不全の悪化→身体所見，胸部X線，体重などに注意。

⑤増量方法，どこまで増量するかは，決まった方針はない→今後の検討課題。

⑥頻度の少ない稀な副作用も多数報告されており専門施設での開始，経過観察が望ましい。

最近の話題

チロシンキナーゼ阻害薬

①イマチニブ：慢性骨髄性白血病の特効薬で副作用の比較的少ない分子標的薬。低濃度で血小板由来血管増殖因子を抑制するため，重症のPAHにも有効。2005年にドイツで報告され，2010年に第Ⅲ相治験が終了した。

②ソラフェニブ：イマチニブでは第Ⅲ相治験において，骨髄抑制などの副作用により投与中止となった症例が40%弱報告されたが，ソラフェニブは皮疹以外の副作用は少なく，効果も高いと思われる。

ガイドライン活用のポイント

▶ガイドラインの要点
①急性血管反応性試験を必ず施行する。
②WHOⅣではエポプロステノールを開始する。
③WHOⅡ，Ⅲでは3系統の治療薬を適宜併用(詳しい方法に関するガイドラインはない)。
▶エポプロステノールの開始時期および増量法，経口治療薬の選択法・併用法についてはガイドラインに示されておらず，今後の検討が求められる。

具体的処方

病型分類	処方例	ポイント
【治療方針】急性血管反応性試験の結果およびWHO心機能分類に従って決定。 【PAH治療薬に共通の副作用】血圧低下，皮膚紅潮，頭痛，下痢。 【併用療法】エポプロステノールが最も有効性の高い薬剤と考えられ，他の内服薬は副作用が許せば可能な限り併用。 【内服薬の使い分け】 ①PDE-Ⅴ阻害薬：自覚的な副作用(上記)がエンドセリン受容体拮抗薬よりやや強い。現在日本では2種が使用可能。シルデナフィルは半減期が短いため1日3回投与する。タダラフィルは半減期が長く長時間型で，副作用や薬物相互作用はシルデナフィルに比較して少ない。どちらの効果が高いかについては今後検討。 ②エンドセリン受容体拮抗薬：2剤が日本で使用可能。どちらの効果が高いかは今後の検討。ボセンタンは，エンドセリン受容体A，B両方の拮抗薬。肝障害・血球減少の副作用がみられるほか，薬物相互作用が多岐にわたる。1日2回投与。アンブリセンタンは，エンドセリン受容体Aの選択的拮抗薬。末梢性浮腫が20〜30%あり薬物相互作用はほとんどない。長時間型で1日1回投与。		
▶急性血管反応性試験陽性	①コニール 4 mg×2回/日，朝夕，血圧が許す限り増量する	①Ca拮抗薬。主に肺動脈攣縮による肺高血圧症を改善。
▶急性血管反応性試験陰性 i) WHOⅣ	①フローラン 1 ng/kg/分より開始，一定の効果が得られるまで増量を持続 最初の2ヵ月間：4日に1度1 ng/分/kgずつ増量 2ヵ月以降：1週間に1度1 ng/kg/分ずつ増量	①PGI_2在宅持続点滴。筆者の施設で施行している一方法を示したが，他施設の方法も参照されたい。 増量の限度は，半年に1度右心カテーテル検査を施行するなどして決定する。増量値の目標は多施設による検討が必要だが筆者の施設では，平均肺動脈40 mmHg未満になるまで週1度の増量を継続している。 副作用，合併症は表4参照。

病型分類	処方例	ポイント
	②レバチオ 20 mg×3回/日，血圧低下例では10 mg/回より開始 またはアドシルカ 10 mg×1回/日，朝に服用 2〜4週後：20 mg/回に増量	②PDE-Ⅴ阻害薬。臓器に特異的な副作用は少ないが，若干の薬物相互作用がある(アドシルカの方が少ない)。フローラン開始前に投与すると，フローランの副作用による心不全の発現・悪化を軽減できる。
	③トラクリア 62.5 mg×2回/日，朝夕に服用 1ヵ月後：125 mg×2回/日に増量 またはヴォリブリス 1回5 mg(2錠)×1回/日，朝に服用 2〜4週後：10 mg/日に増量	③エンドセリン受容体拮抗薬。多剤併用療法を行い，肺高血圧症をできる限り改善して長期予後を良好にする。トラクリアは，開始後2ヵ月間は2週毎，その後は1ヵ月毎に肝機能・血球減少をチェック。多岐にわたる薬物相互作用がある。ヴォリブリスは肝機能障害・血球減少は少ないが，末梢性浮腫を20〜30%で起こす。薬物相互作用もシクロスポリンのみ。
ii) WHOⅢで1)心不全あり，2)心不全の既往あり，3)心不全を早晩起こす肺循環動態，のいずれかに該当	i) と同様に処方する	
iii) WHOⅢで上記ii)に当てはまらないもの	①②i) と同様に処方する ①レバチオ またはアドシルカ ②トラクリア またはヴォリブリス ③ケアロードLA 60 μg(1錠)×2回/日，朝夕に服用，2〜4週毎に1回量を2錠，3錠へと増量	③長時間型ベラプロスト(プロスタグランディン製剤)。フローランより軽微だが同様の副作用がみられる。
iv) WHOⅡ	iii) と同様に処方する	