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EDITORIAL

Treatment of central sleep apnea in patients with heart failure: Now and future

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Abstract

Heart failure (HF) is known to be associated with sleep-disordered breathing (SDB). In addition to disturbing patients' sleep, SDB is also associated with a deterioration in the cardiac function and an increased mortality and morbidity. Central sleep apnea (CSA), typically characterized by Cheyne-Stokes breathing (CSB), is increasingly found in patients with HF compared to the general population. An important pathogenetic factor of CSA seen in HF patients is an instability in the control of the respiratory system, characterized by both hypocapnia and increased chemosensitivity. Sympathetic overactivation, pulmonary congestion and increased chemosensitivity associated with HF stimulate the pulmonary vagal irritant receptor, resulting in chronic hyperventilation and hypocapnia. Additionally, the repetitive apnea and arousal cycles induce cyclic sympathetic activation, which may worsen the cardiac prognosis. Correcting CSB may improve both patient's quality of life and HF syndrome itself. However, a treatment for HF in patients also experiencing CSA is yet to be found. In fact, conflicting results from numerous clinical studies investigating sleep apnea with HF guide to a troubling question, that is whether (or not) sleep apnea should be treated in patients with HF? This editorial attempts to both collect the current evidence about randomized control trials investigating CSA in patients with HF and highlight the effect of specific CSA treatments on cardiovascular endpoints.

Key words: Central sleep apnea; Obstructive sleep apnea; Heart failure; Positive airway pressure; Adaptive servo-ventilation

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Core tip: Central sleep apnea (CSA) is commonly comorbid with heart failure (HF). In fact, sleep apnea is associated with a worsening of the cardiac prognosis and an increasing mortality. However, treatment for CSA remains to be elucidated due to the numerous conflicting results of clinical trials. This review attempts to both clarify the current evidence from randomized control trials investigating CSA in patients with HF and highlight the effect of specific CSA treatments on cardiovascular endpoints.

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INTRODUCTION

Sleep apnea is one of the common complications in patients with heart failure (HF), with reported prevalence rates of 40%-60%[1]. There are two types of sleep apnea, namely obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA is caused by the partial or complete obstruction of the upper airway associated with an attenuation of the upper airway dilator muscle tone during sleep, which is a form of sleep apnea in the general population. In contrast, 25%-40% of patients with HF also experience CSA, with an equal or higher incidence than OSA[1].

CSA seems to be triggered by the hypocapnia associated with pulmonary congestion, by the enhanced chemosensitivity and by the delayed circulation associated with HF itself[2]. Other mechanisms, including overnight fluid shift from the legs to the upper body, may also play a role in the pathogenesis of CSA[3]. Repetitive arousals and episodes of intermittent hypoxia and their associated sympathetic overactivation may lead to further deterioration of the cardiac function, leading to fatal arrhythmia, therefore to poor prognosis. In addition, hemodynamic alterations, especially when occurring during hyperpnea following CSA, may also contribute to the deterioration of the cardiac function[4]. In contrast, considering that alterations in respiration associated with CSA (*i.e.*, repetitive episodes of central apnea and subsequent hyperpnea) were hypothesized to help impaired cardiac pumps and to work as a compensatory mechanism for severe HF, and considering that CSA suppression by either continuous positive airway pressure (CPAP) or adaptive servo-ventilation (ASV) failed to show long-term beneficial effects in clinical trials with patients with both HF and CSA, whether CSA is just an epiphenomenon of HF or a causality of HF is still under debate[5,6].

HF treatment (and its optimization) including beta blockers, angiotensin converting enzyme inhibitors, cardiac resynchronization therapy, left ventricular assist device, cardiac rehabilitation, and heart transplantation are able to alleviate CSA[1]. When CSA remained even under guideline-directed medication towards HF, positive airway pressure (PAP) therapy such as CPAP and ASV will be considered. Numerous observational and short-term randomized controlled trials reported these modalities to have positive effects, showing both an evident alleviation of CSA and a mild improvement of the cardiac function[1]. However, the long-term effects of specific CSA treatments on cardiovascular outcomes remain unclear.

This editorial aims at highlighting the effect of specific CSA treatments on some cardiovascular endpoints in patients with HF by summarizing the results of RCT.

SHORT-TERM EFFICACY OF THE CSA TREATMENT IN HF

In the 1990s and early 2000s, various small-scale randomized control studies identified an effect of the CSA treatment by CPAP on cardiovascular endpoints in patients with HF. In addition, several short-term (0-3 mo) studies reported that CSA treatment by CPAP caused a relative increase (30%) in the left ventricular ejection fraction (LVEF), a reduction in the mitral regurgitation, a decrease in both the overnight urinary norepinephrine (NE) excretion and the daytime NE concentration and an improved quality of life in patients with HF (Table 1)[7-9].

In contrast to CPAP, ASV automatically selects the appropriate support pressure based on the patient's ventilation volume, which is capable of suppressing CSA. In fact, Kasai *et al* performed a short-term analysis and showed that ASV is more capable

Table 1 Short term randomized control trial investigating the effects of continuous positive airway pressure treatment on cardiac functions in heart failure patients with central sleep apnea

Author, year	Duration	*n*	Design	Findings
Naughton, 1995[7]	1 mo	25	no-CSA *vs* CPAP *vs* CSA-control	Urine and plasma NE↓, LVEF↑, NYHA class↓
Naughton, 1995[8]	3 mo	29	no-CSA *vs* CPAP *vs* CSA-control	LVEF↑, improve symptoms
Granton, 1996[30]	3 mo	17	CPAP *vs* CSA-control	MIP↑, LVEF↑, improve symptoms
Tkacova, 1997[9]	3 mo	17	CPAP *vs* CSA-control	LVEF↑, Mitral regurgitant fraction↓, plasma ANP↓

RCT: Randomized control trial; CPAP: Continuous positive airway pressure; HF: Heart failure; CSA: Central sleep apnea; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; NE: Norepinephrine; MIP: Maximal inspiratory pressure; ANP: Atrial natriuretic peptide.

of suppressing CSA and that it improves the cardiac function when compared to CPAP[10]. In addition, Philippe *et al* reported an improvement in patients' quality of life and an increased compliance with ASV when compared to the CPAP treatment group in patients with stable HF (Table 2)[11].

Considering that these investigations suggested beneficial short-term effects on surrogate cardiovascular endpoints, longer follow-up data related to the effects of specific CSA treatments on cardiovascular outcomes are of great interest.

LONG-TERM EFFICACY OF THE CSA TREATMENT IN HF

Small scale RCT by Sin and colleagues (HFrEF, CPAP)

Sin and colleagues conducted a small scale RCT with 66 patients with HF together with or without CSA to investigate the effect of the CPAP therapy. They documented CPAP to both improve the LVEF after 3 mo and to show a trend towards a reduced event rate (P = 0.059, median follow-up period 2.2 years). In addition, CPAP significantly decreased the composite endpoints of death and cardiac transplantation in a subgroup of patients with CSA who were compliant with CPAP (Table 3)[12].

CANPAP (HFrEF, CPAP)

The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP) was a randomized, placebo-controlled clinical trial that involved 258 patients with HF with reduced EF (HFrEF) and CSA. All participants [mean LVEF: 24.5%; apnea-hypopnea index (AHI): 40], after being stabilized to the optimal medical therapy, were randomly allocated to either the control group, that continued the optimal HF therapy, or to the treatment group, that received the CPAP treatment in addition to the optimal HF therapy. They were finally followed for a median of 2.2 years. The treatment group experienced both a greater reduction in AHI (-21 *vs* -2 events/h; P = 0.002) and in daytime plasma NE concentrations (-1 *vs* 0 nmol/L; P = 0.009) and a greater increase in nocturnal oxygen saturation (1.6% *vs* 0.4%; P < 0.001) and LVEF (2.2% *vs* 0.4%; P = 0.016) when compared to the control group. However, the primary outcome related to the transplant-free survival was neutral between the two groups[13]. In contrast, post-hoc analysis of the data from the CANPAP trial showed that patients whose AHI was suppressed lower than 15 events/h by CPAP had a significant improvement in transplant-free survival and in LVEF when compared to the untreated control group (P = 0.043) (Table 3)[14].

These findings suggested that a better suppression of CSA in patients with HF may improve their cardiac outcomes, which increased the clinical demand of ASV (Table 3).

SERVE-HF (HFrEF, ASV)

The Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial was the largest RCT that investigated the effect of the CSA treatment in patients with HFrEF. It involved 1325 patients with predominant CSA and an AHI higher than 15 events/h measured by home polygraphy. Participants were randomly allocated to either the minute volume of ventilation-triggered ASV (mv-ASV) group or to the medical therapy group. The primary endpoint was the composite of death from any cause, including cardiac transplantation, LV assist device (LVAD) implantation, resuscitation after sudden cardiac death, appropriate implanted defibrillator discharge for ventricular arrhythmia, or unplanted admission for worsening HF. Contrary to the expectations, the mv-ASV did not reduce the primary combined

Table 2 Short term randomized control trial investigating the effects of adaptive servo ventilation treatment on cardiac functions in heart failure patients with central sleep apnea

Author, year	Duration	*n*	Design	Findings
Pepperell, 2003[31]	1 mo	30	Therapeutic mv-ASV *vs* subtherapeutic mv-ASV	Plasma BNP↓, urinary metadrenaline↓
Philippe, 2006[11]	6 mo	25	CPAP *vs* mv-ASV	Significant increase in LVEF and improvement in QOL in ASV group
Fietze, 2008[32]	1.5 mo	37	bi-level PAP with standard S/T mode *vs* mv-ASV mode	LVEF increased more in the bi-level PAP group. Daytime blood pressure and heart rate did not change
Kasai, 2013[10]	3 mo	23	CPAP *vs* pf-ASV	LVEF increased more in the ASV group
O'Connor, 2017[21] (CAT-HF trial)[1]	6 mo	126	SDB-control *vs* mv-ASV	No significant cardiac improvement found

[1]CAT-HF trial includes patients with predominant OSA in addition to predominant CSA (> 70% patients had predominant CSA). RCT: Randomized control trial; ASV: Adaptive servo ventilation; CPAP: Continuous positive airway pressure; HF: Heart failure; CSA: Central sleep apnea; OSA: Obstructive sleep apnea; LVEF: Left ventricular ejection fraction; QOL: Quality of life; S/T mode: Spontaneous/timed mode; SDB: Sleep disordered breathing; mv-ASV: Minute volume of ventilation-targeted ASV; pf-ASV: Peak-airflow triggered ASV.

endpoints [hazard ratio (HR) = 1.13, 95%CI: 0.97-1.31; P = 0.10]; however, most importantly, the mv-ASV group showed a significantly increased risk of "all-causes" death (HR = 1.28, 95%CI: 1.06-1.55; P = 0.01) and cardiovascular mortality (HR = 1.34, 95%%CI: 1.09-1.65; P = 0.006) compared to the control group, even though they only represent secondary endpoints (Table 4)[15].

Various arguments were made to explain these unexpected results, including the relatively low usage of mv-ASV, which makes it difficult to interpret the results in an intention-to-treat analysis, and the concerns regarding the first-generation ASV device used in this study, which may have applied an excessive pressure that may reduce cardiac output in some instances.

As noted above, CSA was thought to be detrimental due to intermittent hypoxemia, arousals, and autonomic dysregulation. However, in the largest community-based study, CSA with non-HF conditions did not increase mortality, indicating that CSA itself is not detrimental[16]. Moreover, unexpected findings from the SERVE-HF trial renew the hypothesis stating that CSA may be a compensatory mechanism for HF because alterations in hyperventilation associated with CSA may both help impaired cardiac pumps and work as a compensatory mechanism for severe HF[5], such as increasing end-expiratory lung volume[17], intrinsic positive airway pressure[18], assistance of stroke volume[19], and attenuation of hypercapnic acidosis[20]. Although these effects are seen periodically during CSA, CPAP may provide the similar effects continuously. Nevertheless, although we should be aware that the results of the SERVE-HF trial cannot be applied to patients with different HF statuses, such as HF with preserved EF or predominant OSA, they did affect other RCTs and guidelines dealing with the treatment of patients with HFrEF with predominant CSA. In addition, the trial provided an insight into considering the mechanism underlying each individual HF with CSA, which will be determined in further investigations.

CAT-HF (HFpEF and HFrEF, mv-ASV)

The Cardiovascular Improvements with the mv-ASV Therapy in Heart Failure (CAT-HF) trial was one of the RCTs that was heavily affected by the findings reported by the SERVE-HF trial. This trial attempted to investigate the effects of the mv-ASV on relatively short-term cardiovascular outcomes (*i.e.*, 6 mo) in hospitalized patients with acute decompensated HF and an AHI higher than 15 events/h measured by the hospital polygraphy. The trial was terminated when the SERVE-HF trial results were reported. Interim analysis at the time of termination reported that the mv-ASV showed an absence of between-group difference in terms of the primary outcome (Table 2). However, a prespecified subgroup analysis showed that the mv-ASV can improve disease prognosis in patients with HFpEF[21].

ADVENT-HF (HFrEF, ASV)

Although the negative impact of the SERVE-HF led to the termination of the CAT-HF, further investigations on the effects of sleep apnea treatment by ASV on long-term clinical outcomes are underway. A multi-center RCT assessed the Effects of ASV on

Table 3 Long term randomized control trials investigating the effects of continuous positive airway pressure treatment on cardiovascular outcomes in heart failure patients with central sleep apnea

Author, year	Duration	*n*	Design	Findings
Sin, 2000[12]	2.2 yr (median)	66	No-CSA-control *vs* no-CSA-CPAP *vs* CSA-CPAP *vs* CSA-control	Mortality-cardiac transplantation rate↓ who complied with CPAP, LVEF↑ in CSA-CPAP group
Bradley, 2005[13] (CANPAP trial)	2 yr (mean)	258	CSA-control *vs* CPAP	Plasma NE↓, LVEF↑, distance in a 6-min walk test↑
Arzt, 2007[14] (Post hoc analysis of CANPAP trial)	23 mo (mean)	210	CSA-control *vs* CPAP	Patients whose AHI < 15 events/h by CPAP had significantly improved transplant-free survival and greater improvement in LVEF compared with control

RCT: Randomized control trial; CPAP: Continuous positive airway pressure; HF: Heart failure; CSA: Central sleep apnea; LVEF: Left ventricular ejection fraction; NE: Norepinephrine; AHI: Apnea hypopnea index.

both Survival and Frequency of Hospital Admissions of Patients with Heart Failure and Sleep Apnea (ADVENT-HF) and investigated the effects of the sleep apnea treatment by a peak-airflow-triggered ASV (pf-ASV) on long-term cardiovascular outcomes in patients with HFrEF. In the ADVENT-HF, patients with HFrEF (LVEF 45% or less) and sleep apnea with an AHI of 15 events/h or higher (either predominant OSA or predominant CSA) were enrolled. The primary endpoint is a composite of death, transplantation, LVAD implantation, cardiovascular hospitalization, and out of hospital appropriate defibrillator discharge or new onset of atrial fibrillation with initiation of anticoagulation.

What really distinguishes this study from the SERVE-HF trial is the enrolment and titration of patients using attended, overnight polysomnography. Each sleep study is analyzed at a central lab both to optimize the pressure settings and to ensure the control of sleep apnea. In order to continue the study, its protocol requires both the confirmation of the efficacy of ASV by formal polysomnography and the cessation of active treatment when CSA is not suppressed. In addition, it applies a different device through the nasal interface, providing lower pressure and presumably improving the compliance compared to full-face masks[22,23]. A unique feature of this trial is that either patients with predominant OSA or predominant CSA are enrolled. Despite their differing pathologies, patients with HF can have both types of sleep apnea, and the predominant type can shift from obstructive to central or vice versa[2,24]. OSA may induce CSA with a fall in arterial partial pressure of carbon dioxide and an increase in circulation time, in association with overnight declines in stroke volume and cardiac output[25]. In addition, CSA may lead to upper airway collapses due to inactivation of the upper airway dilatation muscles, in association with attenuation of central respiratory drive, or due to activation of the upper airway constrictor muscles[26]. Thus, in a patient with HF, CSA and OSA may coexist, and effects of treatments for either CSA and OSA, such as ASV on long-term outcome, are quite important. So far, the trial's Data and Safety Monitoring Board (DSMB) did not express ant safety concerns for either CSA or OSA subjects and recommended the continued enrolment of both as per protocol. The ADVENT-HF trial will be a pivotal trial to answer our clinical question, that is whether to treat (or not) sleep apnea in patients with HFrEF.

PERSPECTIVE

Treatment of OSA by CPAP did not show beneficial effects on long-term clinical outcomes in patients with cardiovascular disease. This is probably related to the poor adherence to the CPAP, such as CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea (SAVE) trial, where effects of OSA treatment with CPAP in patients with coronary and/or cerebrovascular disease and with moderate-to-severe OSA were investigated[27]. In addition, in patients with HF, there are no RCTs where effects of OSA treatments with CPAP on long-term clinical outcomes are investigated. Thus, treatment of OSA aiming for secondary prevention of cardiovascular disease remains unelucidated. Similarly, treatment of CSA aiming for the secondary prevention of HF is under debate. In particular, considering the negative results reported by the SERVE-HF trial[15], caution should be maintained when treating

Table 4 Long term randomized control trial investigating the effects of adaptive servo ventilation treatment on cardiovascular outcomes in heart failure patients with central sleep apnea

Author, year	Duration	*n*	Design	Findings
Cowie, 2015[15] (SERVE-HF trial)	31 mo (median)	1325	mv-ASV *vs* CSA-control	All-cause and cardiovascular mortality were both increased in ASV group

RCT: Randomized control trial; ASV: Adaptive servo ventilation; HF: Heart failure; CSA: Central sleep apnea; mv-ASV: Minute volume of ventilation-targeted ASV.

patients with CSA with a LVEF lower than 45%.

As presented in a post hoc analysis from the CANPAP trial, CPAP satisfactorily suppressed more than half of the events in patients with CSA and improved their cardiac prognosis[14]. Up to date, it would be tolerable to prescribe CPAP for CSA in patients with HFrEF and to consider their upgrading to ASV, case by case, when CPAP proves insufficient. In fact, previous short-term studies provided evidence of the positive effects of the ASV treatment for the improvement of the cardiac function or as a biomarker in patients with HF and CSA[26,28], and patients with CSA and HFpEF[29]. Although further investigation is required, the use of ASV should not be abandoned and determining which patients are appropriate and responsive to the ASV treatment should be a priority instead.

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REVIEW

Anatomical backgrounds on gas exchange parameters in the lung

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Abstract

Many problems regarding structure-function relationships have remained unsolved in the field of respiratory physiology. In the present review, we highlighted these uncertain issues from a variety of anatomical and physiological viewpoints. Model A of Weibel in which dichotomously branching airways are incorporated should be used for analyzing gas mixing in conducting and acinar airways. Acinus of Loeschcke is taken as an anatomical gas-exchange unit. Although it is difficult to define functional gas-exchange unit in a way entirely consistent with anatomical structures, acinus of Aschoff may serve as a functional gas-exchange unit in a first approximation. Based on anatomical and physiological perspectives, the multiple inert-gas elimination technique is thought to be highly effective for predicting ventilation-perfusion heterogeneity between acini of Aschoff under steady-state condition. Changes in effective alveolar P_{O2}, the most important parameter in classical gas-exchange theory, are coherent with those in mixed alveolar P_{O2} decided from the multiple inert-gas elimination technique. Therefore, effective alveolar-arterial P_{O2} difference is considered useful for assessing gas-exchange abnormalities in lung periphery. However, one should be aware that although alveolar-arterial P_{O2} difference sensitively detects moderately low ventilation-perfusion regions causing hypoxemia, it is insensitive to abnormal gas exchange evoked by very low and high ventilation-perfusion regions. Pulmonary diffusing capacity for CO (D_{LCO}) and the value corrected for alveolar volume (V_{AV}), *i.e.*, D_{LCO}/V_{AV} (K_{CO}), are thought to be crucial for diagnosing alveolar-wall damages. D_{LCO}-related parameters have higher sensitivity to detecting abnormalities in pulmonary microcirculation than those in the alveolocapillary membrane. We would like to recommend four categories derived from combining behaviors of D_{LCO} with those of K_{CO} for differential diagnosis on anatomically morbid states in alveolar walls: type-1 abnormality defined by decrease in both D_{LCO} and K_{CO}; type-2 abnormality by decrease in D_{LCO} but increase in K_{CO}; type-3 abnormality by decrease in D_{LCO} but restricted rise in K_{CO}; and type-4 abnormality by increase in both D_{LCO} and K_{CO}.

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Key words: Secondary lobule of miller; Acinus of Loeschcke; Acinus of Aschoff; Convection; Gas-phase diffusion (stratification); Aqueous-phase diffusion; Ventilation-perfusion heterogeneity

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Core tip: The anatomical gas-exchange unit is organized into the acinus of Loeschcke, while the functional gas-exchange unit is given by the acinus of Aschoff. The ventilation-perfusion distribution in acinar regions is representatively predicted from the inert-gas elimination technique. The effective alveolar-arterial P_{O2} difference plays a vital role in detecting moderately low ventilation-perfusion regions eliciting hypoxemia but not very low and high ventilation-perfusion regions. Pulmonary diffusing capacity for CO and the value corrected for alveolar volume estimate the impediment of alveolar walls and are more sensitive to detecting the abnormality of pulmonary microcirculation than that of alveolocapillary membrane.

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INTRODUCTION

The morphological and physiological aspects of normal and diseased lungs were most actively studied in the era of the 20th century from the 1950's to the 1980's. The morphological and physiological approaches are both equally important for raising the quality of basic science and of clinical medicine targeting the human lung. Although the lung morphology and the respiratory physiology have evolved in parallel, it is hard to say that the efforts to unite them in a variety of directions by morphologists, physiologists, and clinicians, *i.e.*, the establishment of structure-function relationships, were successful enough. It is of clinical value to understand the anatomical basis of various functional parameters during pathophysiological decision-making in patients with various types of lung disease. Based on these historical facts, we try to shed light on the elucidation of anatomical backgrounds of various functional parameters that have been used for estimating gas maxing in conducting airways and gas exchange in the lung periphery. To accomplish this purpose, the following five matters were comprehensively addressed in the present review: (1) What is the appropriate anatomical design for understanding gas mixing in conducting airways and gas exchange in lung periphery? (2) Aspects of convective and diffusive gas mixing along peripheral airways in a lung model in which dichotomously branching airways are certainly considered. (3) Is the ventilation-perfusion (V_A/Q) distribution in the lung, which is quantitated in terms of the multiple inert-gas elimination technique (MIGET), supported by the anatomical and physiological facts? (4) Is the effective alveolar-arterial P_{O2} difference ($AaDO_2$) estimated from the classical gas-exchange theory also supported by the anatomical and physiological facts? (5) What are the anatomical and physiological determinants on the pulmonary diffusing capacity for carbon monoxide (D_{LCO})?

Anatomical design for understanding gas mixing and gas exchange in the lung

Branching of conducting airways: The pattern of airway branching in a normal lung is best studied on resin or silicon rubber casts[1-8] (Figure 1). The lower conducting airways end in clusters that are surrounded by the fibrous connective tissue septa. The cluster is defined as the secondary lobule of Miller[9,10], which contains lobular (preterminal) bronchioles and terminal bronchioles that supply the gas to or from the acini of Loeschcke[10].

Although conducting airways are most often described as a symmetric tree that branches off by regular dichotomy, in which all pathways have exactly the same length and each generation of branching is composed of airways uniform in size[2,3,11], this type of model is in fundamental conflict with the anatomical facts[2,12,13]. A more realistic representation is a tree of irregular, asymmetric dichotomy, where the dimension of conjugate daughter branches differs from that of their parents. The

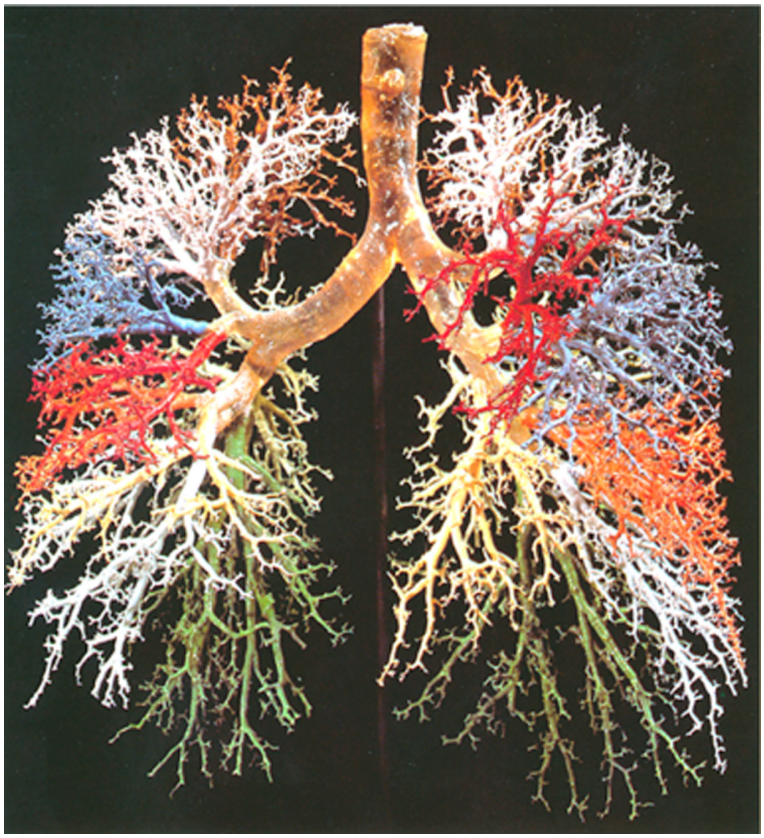


Figure 1 Resin cast of human lung. Complicated dichotomously branching tree of conducting airways is exhibited. Adopted from ref[1].

irregular dichotomy includes different branching angle and varied length-to-diameter ratio at a certain airway generation. Weibel[2,3] demonstrated that the pathway length in airways with 1.5-mm diameter varies between 1.5 mm and 11 mm, with the highest frequency at 3.5-4.0 mm. Similarly, airways of 2.0 mm in diameter (*i.e.*, small airways) are spread out between the 4th and 14th generations of the branching tree, with a maximum at the 8th generation. The valuable message emanating from the studies of Weibel is that although conducting airways are correctly modeled by an irregular, asymmetric dichotomous branching tree, the dimensional variation of airway diameters and path lengths assigned to each generation of the tree nearly follows the normal distribution, and this variation decreases as the generation progresses. Based on these findings, a simple design called "model A of Weibel"[2,3] or "typical path lung model"[4,5,14] has been developed. This model assumes that in an initial approximation, the asymmetric branching tree can be replaced by the symmetric branching tree using the mean (representative) value estimated from the normal distribution of airway diameters as well as that of path lengths at a given generation (Figure 2), which results in that one can assess gas mixing in the conducting airways with asymmetric branches from the model A of Weibel with simple geometry.

Anatomical definition of lobule and acinus: Different terms have been used for defining the lobule and the acinus throughout several decades. In 1947, Miller proposed the anatomical concept that is valuable for understanding the secondary and primary lobules[9]. As described above, the secondary lobule of Miller is the unit supplied by a lobular bronchiole having a diameter of about 1.0 mm (corresponding to the 12th generation) and surrounded by the fibrous connective tissue septa (*i.e.*, the interlobular septa) (Figure 3). The size of secondary lobules of Miller varies from 1.0 cm to 2.5 cm, each of which is comprised of varying numbers of acini defined by Loeschcke, ranging from three to twenty-four depending on the region selected[15,16]. On the other hand, the primary lobule of Miller is expressed by the area governed by an alveolar duct. The secondary lobule proposed by Miller has various advantages from anatomical points of view. Therefore, unless otherwise specified, the simple term of "secondary lobule" is used in the sense of "secondary lobule of Miller" throughout the current review.

In 1958, based on the bronchogram of peripheral airways, Reid[17,18] presented a different definition with regard to the secondary lobule. The secondary lobule of Reid

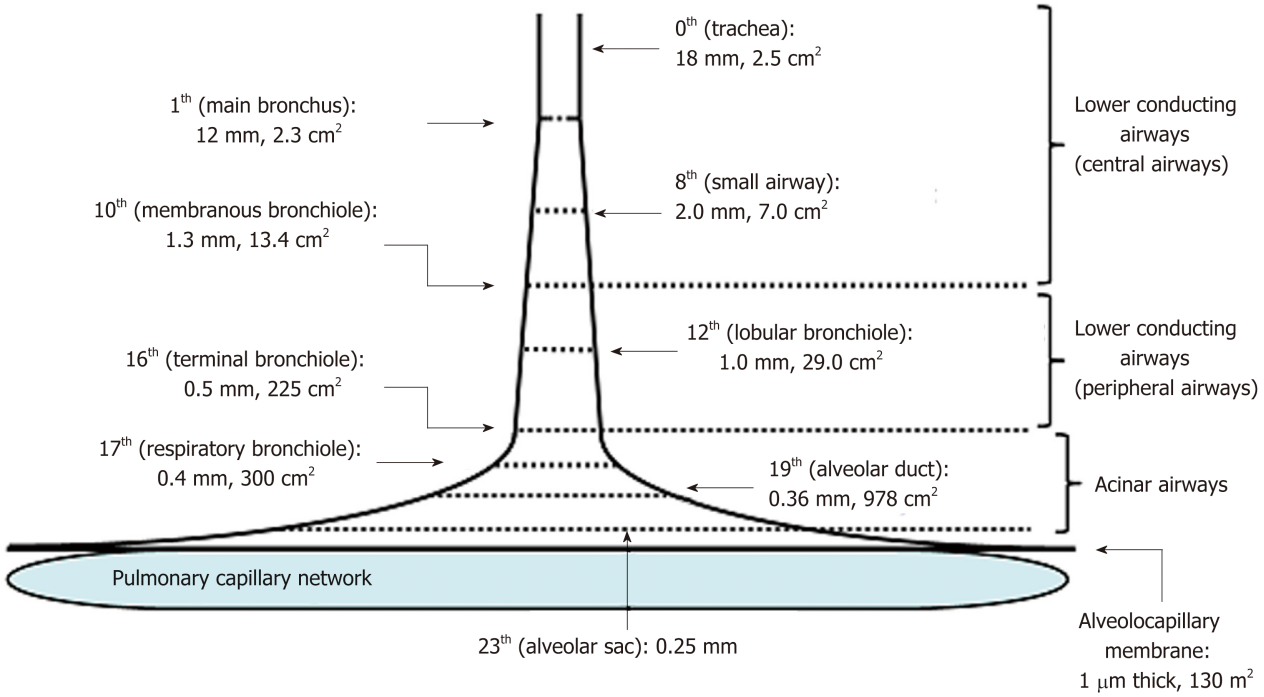


Figure 2 Schematic presentation of effective diameter and cross-sectional area along lower conducting airways and acinar airways (trumpet or thumbtack model). Generations of branching tree and diameter as well as cross-sectional area in each generation are obtained from model A of Weibel[2]. Lower conducting airways are classified into two routes; *i.e.*, central airways [generation from zero (trachea) to 9th] and peripheral airways (generation from 10th to 16th, in which 16th generation corresponds to terminal bronchiole). Peripheral airways are characterized by membrane bronchioles, whereas small airways are defined by their diameters of less than 2.0 mm originating in the 8th generation. Airways from the 17th generation (respiratory bronchiole) to the 23th generation (alveolar sac) are not included in peripheral airways. Instead, they are defined as acinar (alveolated) airways (acinus indicates that defined by Loeschcke). This is because acinar airways function by carrying gas and exchanging gas. Alveolar sacs end in alveoli formed by alveolar walls containing alveolocapillary membranes and capillary networks. Thickness of the alveolocapillary membrane is about 1.0 μm and total cross-sectional area of the alveolocapillary membrane and capillary network is about 130 m^2.

is the unit formed by the structure distal to any bronchiole having a mm-branching pattern. The size of the secondary lobule of Reid is fairly constant (approximately 1.0 cm) in comparison with that of Miller and contains three to five acini of Loeschcke. The Reid's definition is more useful when interpreting the bronchogram.

The acinus of Loeschcke is the unit distal to a terminal bronchiole (Figure 3), in which all alveolated airways engage in gas exchange. The size of the acinus of Loeschcke averages 7 mm to 10 mm in diameter and roughly 80000 acini configure the lung. An acinus contains alveoli ranging from 3000 to 4000[8,19], resulting in the lung consisting of 300-million alveoli.

The acinus of Aschoff is defined as the area supplied by a first-order respiratory bronchiole (Figure 3), the size of which is half of the acinus of Loeschcke[20]. All alveolated airways in the acinus of Aschoff participate in gas exchange. The acinus of Loeschcke is important when defining the anatomical gas-exchange unit, while the acinus of Aschoff is important when the functional gas exchange is defined.

Similar to conducting airways, intra-acinar, alveolated airways (respiratory bronchioles, alveolar ducts, and alveolar sacs) also show irregular dichotomous branching over an average of nine generations, terminating at between the 6th to 12th generations[8,21,22]. Large acini have more generations and smaller acini have correspondingly fewer. Although the issue of whether the variation of airway diameters and path lengths of each generation in the acinus (Loeschcke or Aschoff) follows the normal distribution has not been reliably concluded, Weibel and colleagues[2,3,8] presumed that the geometrically-simple model A of Weibel could be applied for integrating the branches of conducting airways and acinar airways. The features of model A of Weibel (Figure 2), which is also called the "trumpet model" or "thumbtack model", are summarized as follows[2,23,24]: (1) the model consists of the average number of generations over which the airways must terminate in the alveolar sacs corresponding to the 23th generation; (2) the 16th generation defines the terminal bronchiole; (3) the 17th-22th generations correspond to the acinar airways, including the respiratory bronchioles and alveolar ducts; and (4) the number of airways in a particular generation increases tremendously as the generation increases, leading to the exponential increase in the generation-specific total cross-sectional area. Weibel[2]

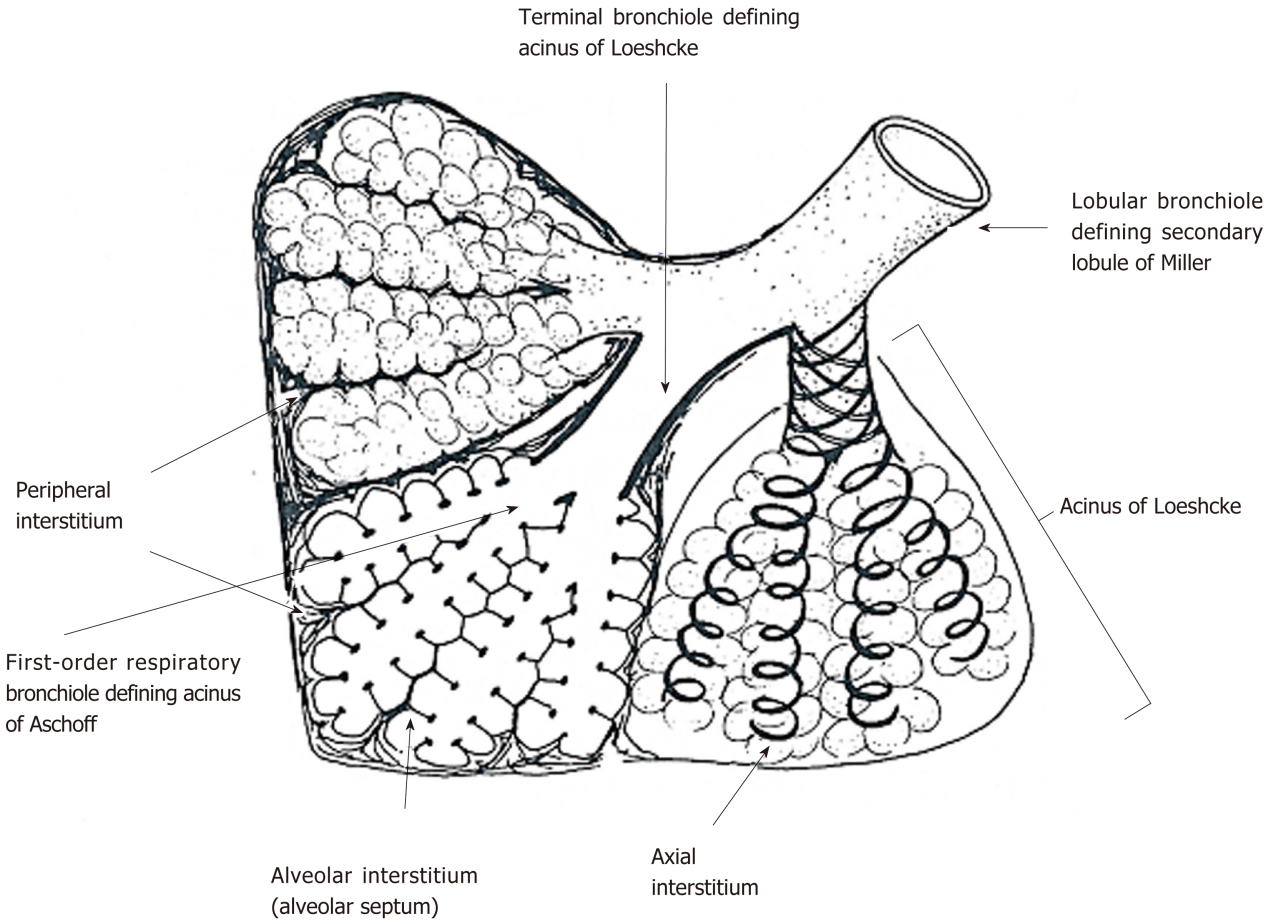


Figure 3 Secondary lobule and acinus. Secondary lobule of Miller is defined by the area supplied by a lobular bronchiole while the acinus of Loeschcke is defined by the area supplied by a terminal bronchiole. Acinus of Aschoff is the area supplied by a first-order respiratory bronchiole. Secondary lobule of Miller is surrounded by fibrous connective tissue forming interlobular septum. In acini of Loeschcke and Aschoff, there are three important interstitial tissues, including peripheral interstitium, alveolar interstitium forming alveolar septum, and axial interstitium spirally surrounding airways, which begins at the alveolar duct extending to the hilum. Axial interstitium and alveolar interstitium are joined via intra-parenchymal interstitium and all interstitial tissues are in a serial linkage. Modified from ref[2].

demonstrated that the average diameter of terminal bronchiole, respiratory bronchiole, or alveolar duct is 0.50 mm, 0.39 mm, and 0.33 mm, respectively, while the average total cross-sectional area of these airways is 230 cm^2, 420 cm^2, and 2630 cm^2 (equal to 0.263 m^2), respectively. The total cross-sectional area including all alveoli amounts to about 130 m^2 in association with the harmonic mean thickness of alveolocapillary membrane of 1.1 μm[25].

Anatomical aspects of collateral ventilation: Three pathways exist for collateral ventilation in the acinus, *i.e.*, alveolar pores (pores of Kohn), channels of Lambert, and channels of Martin. Although the typical size of alveolar pores ranges from 2 μm to 30 μm, there have been many anatomical, physiological, and theoretical studies leading to the conclusion that the alveolar pores are not potent in air-filled lungs[26,27]. These studies indicate that the alveolar pores take no part in maintaining alveolar ventilation.

In 1955, Lambert[28] described accessory communications between bronchioles and alveoli in the normal human lung. The diameter of Lambert channels varies from 0 μm (practically closed) to 30 μm, and they are considered to serve as collateral ventilation to adjacent alveoli when airway obstruction occurs at the level of terminal bronchioles[27]. Supporting this consideration, the important role of Lambert channels was identified in patients with pneumoconiosis, in which a striking accumulation of macrophages was found in the Lambert channels and their adjacent alveoli[29].

In 1966, Martin[30] reported intra-acinar communications at the level of respiratory bronchioles or alveolar ducts in the canine lung. The Martin channels were found in human lungs as well[9,31]. As the Martin channels have sufficiently low resistance to gas flow, they act as the primary pathway for inducing collateral ventilation in the acinus[27]. Therefore, one can conceive that only the Martin channels but neither the alveolar pores nor the Lambert channels serve to equalize the distribution of alveolar

ventilation and the concentration of a certain gas in a particular acinus, though the extent of equalization elicited by collateral ventilation has not been conclusively quantified.

Definition of anatomical gas-exchange unit – importance of acinus of Loeschcke: The alveolus cannot be taken as a ventilation unit mostly because each alveolus is not independent of other alveoli. Two adjoining alveoli share the alveolar wall and each alveolus adjoins several alveoli, some of which are connected to different alveolar ducts. Furthermore, there are communications at the level of respiratory bronchioles or alveolar ducts (Martin channels). On the other hand, the acinus of Loeschcke can be taken as an anatomical ventilation unit because it is supplied only by a single conducting airway with no alveoli, *i.e.*, the terminal bronchiole (Figure 3).

There is a serious problem concerning a perfusion unit formed by the pulmonary microcirculation. The dense, intertwined capillary network embedded in the alveolar wall forms a continuum of blood flow that is not partitioned into independent perfusion units. This disproves that the gas-exchange unit is organized into an alveolus associated with a separated capillary network in the alveolar wall. The capillary network is supplied by the arteriole that penetrates into the acinus along the acinar airways and is drained into the venule in the acinar periphery. The distance between an arteriole and a venule is of an order between 0.5 mm and 1.0 mm[32], suggesting that the perfusion unit given by the area surrounded by an arteriole and a venule extends over several alveoli, but it does not cover the whole area of an acinus of Loeschcke whose size ranges from 7 mm to 10 mm[25]. These facts are in accord with the idea that the perfusion unit is not congruent with the ventilation unit so that it gives rise to difficulty in anatomically defining the gas-exchange unit in which the ventilation and perfusion units should be matched. However, König *et al*[33] found that the whole acinar region of Loeschcke is perfused almost homogeneously by colloid gold used as a plasma tracer even at rest, indicating that all capillary networks existing in the acinus of Loeschcke are connected to each other. Based on the study of König *et al*[33], we considered that the anatomical gas-exchange unit is organized approximately into the acinus of Loeschcke.

Convective and diffusive gas mixing in conducting and acinar airways

In addition to the convective mixing elicited by ventilation, the diffusive mixing plays an important role in maintaining gas transport along peripheral and acinar airways with large cross-sectional areas (Figure 2). Numerous mathematical attempts have been made to estimate the effect of convection, diffusion, or interactions of both on gas transport in conducting and acinar airways using a model with symmetrically or asymmetrically dichotomous branching of airways[24]. The term of convection is defined as a mass transport resulting from the unidirectional displacement of molecules included in a certain volume. Convective displacement is identical for all molecular species and is not different for gases with different diffusivity. This indicates that convection (laminar or turbulent flows) occurs along gradients of total pressure but not along those of partial pressure.

On the other hand, the term of diffusion is defined as a result from the random motion of molecules due to their thermal energies, depending on their concentration (partial pressure) gradients and diffusivity. Hence, a separation of two gases with different diffusivity occurs during gas transport when diffusive transport constitutes a main limiting process, whereas a separation of two gases is not investigated when gas transport is mainly limited by convection. Diffusive transport in airways and alveoli occurs in axial and radial directions; yet the mechanism of these two directions is the same. Furthermore, the coupling of convection and diffusion occurs under a condition where the contribution of convection and diffusion to gas transport is of similar magnitude, which may occur predominantly in peripheral airways at generations between the 8th and 12th[34]. The magnitude of convection-diffusion coupling under a condition of laminar or turbulent flow is estimated using the dispersion coefficient proposed by Taylor and others[35-38]. However, the Taylor dispersion has been identified to be insignificant for gas transport during normal breathing[39-43], leading to the conclusion that it is enough to introduce only the convection and diffusion (particularly, axial diffusion), but not the dispersion, as the basic mechanism when assessing the gas transport along conducting and acinar airways.

Introducing both convection and diffusion as the gas mixing mechanism into model A of Weibel that has a simple geometry with trumpet or thumbtack shape, several groups of investigators analyzed the time-dependent change in gas concentration profile of an insoluble gas that is not absorbed into the blood (*i.e.*, no gas exchange) along peripheral conducting airways and acinar airways during normal breathing[39,44-50]. Paiva[46] assumed: (1) no dispersion in airways; (2) no radial diffusion

in airways; (3) no axial diffusion in alveolar regions; (4) no convective flow in alveolar regions (*i.e.*, alveoli simply act as a sink for diluting a gas during inspiration while as a reservoir for expelling a gas during expiration); and (5) no collateral ventilation in acinar regions. As the theoretical calculation by Paiva[46] was made under a situation where the tidal volume was set at 500 mL and the functional residual capacity at 3000 mL (*i.e.*, the representative lung volume during normal breathing), the end-inspiratory gas concentration in the alveolar region is reduced to 17% of that at the beginning of inspiration. Paiva[46] analyzed gas mixing kinetics along airways constituting the last 13th generations, which correspond closely to the secondary lobule of Miller (Figures 2 and 3). The results emphasized by Paiva[46] are summarized below (Figure 4):

(1) On inspiration, the front of a gas, which is expressed by the axial distance at which the concentration of a gas is reduced to 50% of the value at the beginning of inspiration, lags appreciably behind the front of tidal volume. The front of tidal volume attains to the 22th generation of airways (*i.e.*, the alveolar duct), whereas the front of a gas stays at the 17th generation (*i.e.*, the first-order respiratory bronchiole defining the acinus of Aschoff). The gas front is practically stationary, suggesting that the convective advancement of a gas into the periphery is counterbalanced by the diffusion-elicited proximal retreat of a gas. The volume from the airway entrance to the gas front is about 150 mL, which corresponds to the common dead space volume conceptualized in the classical gas-exchange theory. This indicates that the classical, common dead space can be defined as the inspiratory volume decided by the gas front, but not by the front of tidal volume. Furthermore, the classical gas-exchange theory assumes that the front of common dead space has a sharp, all-or-nothing transition boundary as if it is formed only by the ventilation-induced convective flow, implying that the effect of diffusion is converted to the equivalent effect of convection. The region distal to the boundary is the alveolar region in which gas exchange takes place. The definition of dead space specified by Paiva[46] issues an important message as to the way of how to define the functional gas exchange unit in the steady-state V_A/Q analysis and classical gas exchange theory, both of which will be argued in the following sections.

(2) On expiration, all intrapulmonary concentration gradients of a gas are rapidly faded out, which is mainly caused by the thoracic shrinkage-induced convective flow during expiration. The diffusive process in acinar gas phase imposes a negative impact on gas transport in an early stage, but not in a later stage, of expiration. The aforementioned findings during one respiratory cycle indicate that the stratification (*i.e.*, the concentration gradient of a gas due to diffusion) is evident along acinar airways during inspiration but is minimal during expiration. Differing from inspiratory phase, the common dead space formed by the non-alveolated, conducting airways exerts nearly no impact on gas transport in conducting airways during expiratory phase. Instead, the common dead space literally functions as a simple reservoir for diluting the gas expelled from all alveolar regions during expiration.

Quantification of continuous distribution of V_A/Q

Definition of functional gas-exchange unit – importance of acinus of Aschoff: In general, the continuous distribution of V_A/Q in the lung has been quantitated by means of the MIGET. The most important matter in the MIGET is how to define the functional gas-exchange unit in which concentration of a gas should show uniform value. Although the acinus of Loeschcke approximates the anatomical gas-exchange unit, it is uncertain as to the issue of whether the acinus of Loeschcke concurrently serves as the functional gas-exchange unit. In the acinus of Loeschcke, an alveolus adjoins several alveoli and there are communications at the level of respiratory bronchioles or alveolar ducts (Martin channels), both of which tend to equalize gas-concentration difference over the acinus of Loeschcke. However, the point of whether the equalization of gas concentration in the acinus of Loeschcke is complete has not been confirmed. Therefore, it may be fraught with the problem to blindly adopt the acinus of Loeschcke as the functional gas-exchange unit.

In fact, Paiva *et al*[51] suggested that the regions distal to the alveolar duct, which correspond to the primary lobules of Miller, have different gas concentrations at the end of inspiration after a single-breath of a non-absorbable gas. However, they[51] also demonstrated that the gas-concentration difference between respective primary lobules of Miller formed during inspiration diminishes rapidly during expiration. Furthermore, caution should be paid to the fact that Paiva *et al*[51] disregarded the effect of Martin channels-induced collateral ventilation on gas-concentration equalization between the primary lobules of Miller. If the collateral ventilation-elicited equalization effect is taken into consideration, the gas-concentration difference between the primary lobules of Miller is expected to become much smaller. The importance of the acinus of Aschoff given by the region distal to the first-order

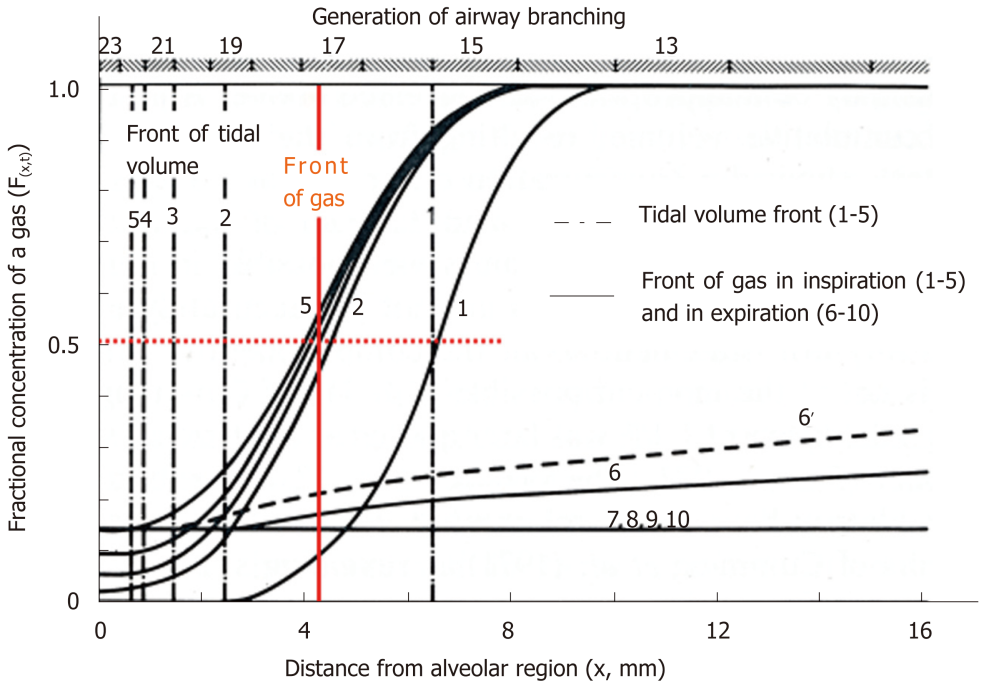


Figure 4 Concentration profiles along peripheral conducting airways and acinar airways during the respiratory cycle in thumbtack model. Upper abscissa: generation of airway branching defined in model A of Weibel. Lower abscissa: axial distance from alveolar region. Ordinate: fractional concentration of the test gas. 100% O_2 is inhaled (single breath) into and then exhaled from initially O_2-free lung with constant flow (tidal volume: 500 mL) and constant lung volume (functional residual capacity: 3000 mL). O_2 is assumed to not be absorbed into capillary blood (*i.e.*, no gas exchange). Solid curves (black) indicate concentration profiles at successive equally timed periods during inspiration (1-5) and expiration (6-10). Dashed dotted lines (1-5) are tidal volume fronts (*i.e.*, concentration fronts of non-diffusible tracer gas) during inspiration. Dashed line (6') is a concentration profile calculated on assumption of no axial diffusion during expiratory phase corresponding to time point of solid line (6). Red solid line denotes "imaginary" boundary between common dead space and alveolar region conceptualized in classical gas-exchange theory. Boundary is defined by stationary gas front converting diffusional effect into equivalent convectional effect, which is formed at entrance of acinus of Aschoff (17th generation of branching tree). See text for detailed explanation. Modified from ref[46].

respiratory bronchiole as the functional gas-exchange unit was implicitly indicated by Paiva[46]. He showed that the "imaginary" boundary separating the alveolar gas-exchange region from the dead space exists in the vicinity of the first-order respiratory bronchiole corresponding to the entrance of the acinus of Aschoff (Figures 3 and 4). As such, the study of Paiva[46] suggests that the functional gas-exchange unit under a steady-state condition is close to the anatomically defined acinus of Aschoff. This is because the size of the acinus of Aschoff is about half of the acinus of Loeschcke such that the gas-concentration variation, if any, is much smaller between the acini of Aschoff than that between the acini of Loeschcke. This results in that the acinus of Aschoff satisfies the essential requirement for the functional gas-exchange unit, namely the uniformity of gas concentration over the unit, more precisely than the acinus of Loeschcke does. Hence, we considered that the functional gas-exchange unit should be defined by the acinus of Aschoff whose area is smaller than that of the anatomical gas-exchange unit formed by the acinus of Loeschcke, leading to the conclusion that the MIGET argued in this section should be thought to predict the V_A/Q heterogeneity between the acini of Aschoff.

Basic rationale for determining V_A/Q distribution: Under a steady-state condition in which there is no change in the partial pressure of a gas (P) against the elapsed time (t) at any portion of the lung (*i.e.*, $\Delta P/\Delta t$ = zero), the partial pressure of an inert gas in gas phase (P_A) and that in blood phase (P_c) of a given functional gas-exchange unit are described by the simple equation in accordance with the law of mass balance[19,52-54].

$P_A/P_v = P_c/P_v = \lambda/(\lambda + V_A/Q)$ ····· eq. 1

Where P_v denotes the partial pressure of a given inert gas in mixed venous blood, whereas λ is the blood-gas partition coefficient of a gas, which is decided by its blood solubility (α)[19,55]. The eq. 1 is approved only in a condition where the inspired air does not contain any trace of an inert gas. This holds true when an inert gas is infused through the peripheral vein but not when it is inhaled through the mouth. The eq.1 implies that the partial pressure of an inert gas in the functional gas-exchange unit is simply determined by the ratio of convective flow of ventilation (V_A) and that of perfusion (Q) distributed to each functional gas-exchange unit. There are many

physiological assumptions that should be addressed for the establishment of eq. 1[19,54,56-59]. They are listed below.

(1) The functional gas-exchange unit is in a steady state such that the net transfer rate of an inert gas from capillary blood to alveoli in the functional gas-exchange unit exactly equals the net rate of elimination through expiration. Thus, the amount of an inert gas stored in blood, lung tissue, or alveoli is constant. The condition in which the MIGET is applied meets the steady-state definition.

(2) The tidal nature of ventilation is ignored. Namely, the rebreathing of a gas fulfilling the common dead space in previous expiration is not considered. The MIGET assumed the specific, personal dead space connecting to the individual functional gas-exchange unit. Therefore, in the next inspiration, each functional gas-exchange unit inhales the gas from each personal dead space that has the same gas composition as that expelled from each functional gas-exchange unit in the previous expiration. This assumption is highly dissociated from the anatomical and physiological facts. However, the volume of common dead space configured by upper and lower conducting airways amounts to 150 mL, which corresponds to only 5% of the lung volume represented by the functional residual capacity (3000 mL), suggesting that the gas contained in the common dead space is diluted largely when it reaches the gas-exchange units at an early stage of the next inspiration. Furthermore, the inspiratory tidal volume is 500 mL so that after inhaling the gas remaining in the dead space (150 mL), which is the averaged mixed alveolar gas exhaled from all functional gas-exchange units during previous expiration, an inspired gas with no inert gas refreshes the gas-exchange units in a later stage of inspiration (350 mL). These considerations suggest that the averaged inert-gas concentration at the entrance of functional gas-exchange unit during inspiration is almost zero under a condition where the MIGET is applied.

(3) The pulsatile nature of blood is disregarded so that capillary blood flow is taken to be continuous. Bidani *et al*[60] analyzed the effect of pulsatile flow (Q_C) and pulsatile capillary blood volume (V_C) on equilibration of O_2 between capillary blood and alveolar gas. They found little difference in O_2 equilibration profile between the condition where both Q_C and V_C are constant and the condition where both Q_C and V_C have pulsatile natures. Therefore, the assumption of constant blood flow may derive no discernable distortion regarding the steady-state gas exchange[61].

(4) The functional gas-exchange unit is assumed to receive capillary blood flow with the same hematocrit. As first suggested by Brisco[62], the gas solubility in erythrocytes is different from that in plasma, indicating that variation in hematocrit between capillaries may affect inert-gas exchange to some extent. However, Young and Wagner[63] demonstrated that although the inert-gas solubility is influenced appreciably by misdistribution of hematocrit, its effect on inert-gas exchange is small.

(5) The inert-gas solubility is taken to be constant irrespective of oxygen saturation with hemoglobin (Hb) (SO_2) and blood pH. Yamaguchi *et al*[64] experimentally demonstrated that SO_2 has no impact, while blood pH has a substantial impact, on the inert-gas solubility, including ethane and cyclopropane, both of which are confined to the protein fraction of blood. However, in the same paper, Yamaguchi *et al*[64] demonstrated that the effect of pH-dependent change in blood solubility of either ethane or cyclopropane on recovered V_A/Q distribution is small.

(6) Diffusion equilibration is assumed to be complete. This assumption applies both to the diffusion between capillary blood and gas phase through alveolocapillary membrane (aqueous-phase diffusion) and to the diffusion within gas phase [gas-phase diffusion (stratification)]. The blood-gas equilibration is valid for any inert gas that does not combine with Hb[52]. However, this assumption is invalid while analyzing the gas combining with Hb, especially carbon monoxide (CO) and nitric oxide (NO)[65].

As argued in the previous section, the stratification is evident in inspiration but not in expiration (Figure 4). Since the MIGET analyzes the gas only collected during expiration, the assumption that the stratification has little impact on gas transfer may be approved in the MIGET condition. Furthermore, Yamaguchi *et al*[66] demonstrated that excepting severe acute respiratory distress syndrome, the stratification plays no role during inert-gas elimination under the condition similar to that of the MIGET. The detailed discussions expanded above identified that most of the physiological assumptions introduced by the MIGET have correct grounds.

Determination of continuous distribution of V_A/Q: Saline containing a small quantity of six foreign inert gases with a wide variety of λ, including sulfur hexafluoride (SF_6) (λ = 0.009 mL/mL at 37 °C), ethane (λ = 0.09), cyclopropane (λ = 0.58), halothane (λ = 2.82), diethyl ether (λ = 14.4), and acetone (λ = 304) was infused through the peripheral vein at a constant rate of 2 mL/min[54,56]. After steady state was established (about 30 min after initiating infusion), expired gas, arterial blood, and

mixed venous blood were simultaneously sampled and the concentrations of six inert gases in the samples were measured by gas chromatography equipped with flame ionization for hydrocarbons and electron capture for SF_6[67]. Using the data measured for six inert gases, Wagner and colleagues[56,58,59] established a novel method allowing for predicting a continuous distribution of V_A/Q in a representative manner. In this method, they assumed the 50 functional gas-exchange units with a variety of V_A/Q values, including the right-to-left shunt with V_A/Q of zero (the number of functional gas-exchange unit: 1), the dead space with infinite V_A/Q (the number: 50) composed of series (common) and parallel (alveolar) dead space, and the 48 units with finite values of V_A/Q ranging from 0.005 to 100, all of which are arranged in parallel and are equally spaced on a logarithmic scale. Applying the least-squares minimization coupled with enforced smoothing under non-negativity constraints for V_A and Q, they determined the distribution of V_A and/or Q along the logarithmic V_A/Q axis. However, it should be noted that the lung model adopted by Wagner *et al*[56,58,59] consists of unknown variables whose number (n = 50) greatly exceeds the number of measured variables (n = 6) so that no unique solution is generally obtainable[68,69]. In principle, the greater the number of gases, the more detailed and precise is the resultant estimate of the V_A/Q distribution. To solve the problem of a non-unique solution, Evans and Wagner[69-73] introduced the linear programing approach, in which the upper limit of V_A and/or Q distributed to a certain V_A/Q unit was examined based on the error of each inert-gas measurement. The linear programming can reliably decide the issue of whether the V_A/Q distribution is unimodal or contains more than one mode, *i.e.*, bimodal or trimodal. The mode of V_A/Q distribution representatively determined by the least-squares minimization was shown to be qualitatively coincident with that by the linear programming[70] (Figure 5). Furthermore, Wagner and West[59,74-76] analyzed the matching between the measured arterial P_{O2} (P_{aO2}) and that predicted from the representative V_A/Q distribution. They found a satisfactory agreement between the two values in patients with chronic obstructive pulmonary disease (COPD) and interstitial pneumonias at rest (Figure 6). However, Wagner[76] found that the P_{aO2} predicted from the MIGET is appreciably higher than the measured P_{aO2} in patients with interstitial pneumonias under an excise condition. This indicates that in addition to the V_A/Q heterogeneity, the aqueous-phase diffusion limitation through alveolocapillary membrane plays some role in worsening hypoxemia during exercise in patients with interstitial pneumonias.

The representative distributions of V_A/Q in normal subjects as well as patients with interstitial pneumonia and COPD are depicted in Figure 7[59]. A normal subject revealed the unimodal distribution of V_A and Q along the V_A/Q axis, which resembles the sharp normal distribution. A patient with interstitial pneumonia showed the bimodal V_A/Q distribution with low V_A/Q regions associated with augmented right-to-left shunt. The formation of low V_A/Q regions and shunt may be ascribed to the interstitial fibrosis-elicited destruction of acinar structures. A COPD patient with predominant emphysema showed the bimodal V_A/Q heterogeneity with high V_A/Q regions, which may be attributed to the regional hyperventilation caused by the destruction of alveoli. A patient with predominant bronchiolar involvements revealed the bimodal V_A/Q heterogeneity with low V_A/Q regions, which may be caused by the destruction and/or obliteration of acinar bronchioles.

Based on the V_A/Q-D/Q concept developed by Piiper[77], in which D denotes the aqueous-phase diffusing capacity for O_2, CO_2, or CO through alveolocapillary membrane, Yamaguchi *et al*[66,78-80] elaborated a novel method that allows for predicting the continuous distribution of V_A/Q and D/Q under a steady-state condition. They[66,78-80] found that in addition to the V_A/Q heterogeneity, the D/Q heterogeneity is expanded in patients with interstitial lung diseases but less evident in patients with COPD (Figure 8). Therefore, it was conceived that the heterogeneity of aqueous-phase diffusion plays some role in impeding gas exchange, particularly in lungs with destruction of alveolocapillary membrane or pulmonary microcirculation.

$AaDO_2$ in classical gas-exchange theory

Determination of alveolar gas composition: About 100 years ago, Krogh *et al*[81] first described the important principle in the field of respiratory physiology; namely, the gas exchange taking place in any lung region is determined by neither the ventilation nor the blood flow but by the ratio of one another. Shortly after this, Haldane[82] recognized that ventilation-perfusion heterogeneity could cause hypoxemia. These pioneering works led Fenn *et al*[83], Riley and Cournand[84], and others into the establishment of classical gas-exchange theory in a more precise fashion. Rahn[85] proposed the concept of "mean alveolar gas" while Riley *et al*[84,86] proposed the concept of "ideal alveolar gas". These two terms are physiologically identical and defined as the intersection of blood and gas R lines, in which R is the respiratory gas-exchange ratio given by the ratio of CO_2 production (V_{CO2}) to O_2 consumption (V_{O2}) of

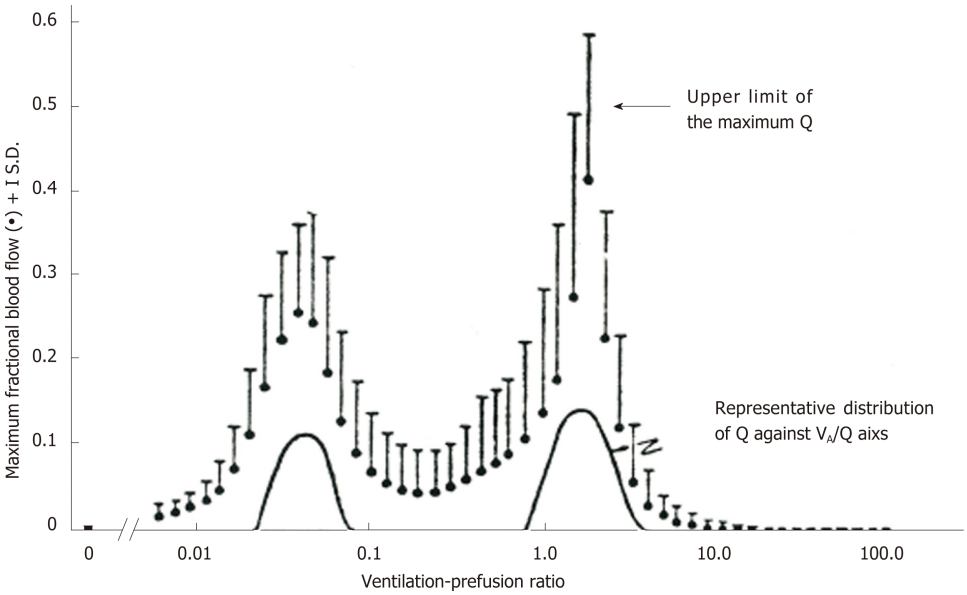


Figure 5 Range of solution for ventilation-perfusion distribution recovered from multiple inert-gas elimination technique. Comparison between representative perfusion distribution obtained from multiple inert-gas elimination technique in terms of least-squares minimization and maximum perfusion distribution decided by linear programming. Adopted from ref[70].

the whole body (Figure 9). As the R is identical at any portion of the body under a steady-state condition, the R values at the level of capillary blood (blood R line) and alveolar gas (gas R line) are the same as that of mixed expired gas. It was theoretically identified that the intersection of the blood R line and gas R line defined the single V_A/Q value and the corresponding unique pair of P_{O2} and P_{CO2} in alveolar gas and capillary blood of a certain lung (the O_2-CO_2 diagram or the V_A/Q line[61,87])[84-86]. Although the P_{O2} and P_{CO2} values thus determined satisfactorily meet the metabolic state of the whole body, it does not secure that these P_{O2} and P_{CO2} can work as the representative indicator while analyzing the gas-exchange behavior in the lung. This is because the concept of mean (ideal) alveolar P_{O2} and P_{CO2} is largely lacking in the considerations on complicatedly intertwined lung anatomy and intricate physiological gas-transfer mechanism along the airways and in the lung periphery. Furthermore, to calculate the mean (ideal) alveolar gas, it is necessary to measure P_{O2} and P_{CO2} in mixed venous blood. As this procedure is cumbersome in a clinical setting, Riley *et al*[86] proposed a new concept of "effective alveolar gas," in which the mean (ideal) alveolar P_{CO2} is taken to equal the arterial P_{CO2} (P_{aCO2}). Because of the relative flatness of blood CO_2 dissociation curve under a physiological condition, the difference between mean (ideal) P_{CO2} and P_{aCO2} is remarkably small (Figure 9), which indicates that it is not unreasonable to use P_{aCO2} in place of mean (ideal) alveolar P_{CO2}. Therefore, P_{aCO2} is defined as "effective alveolar P_{CO2}" and alveolar P_{O2} estimated therefrom is called "effective alveolar P_{O2}". As it is not necessary to measure the gas pressures in mixed venous blood, the concept of effective alveolar P_{O2} has received a great deal of support from physicians, though the anatomical and/or physiological validations on effective alveolar P_{O2} have been lacking. Based on the simplified form of alveolar gas equation, the effective alveolar P_{O2} (effective P_{AO2}) is calculated as

Effective $P_{AO2} = P_{IO2} - P_{aCO2}/R$ ····· eq. 2

Where P_{IO2}, P_{aCO2}, and R denote inspiratory P_{O2}, arterial P_{CO2}, and respiratory gas-exchange ratio, respectively. The R value is taken to be 0.83 in general.

Using eq. 2, one can easily predict the effective alveolar-arterial P_{O2} difference (effective $AaDO_2$) at the bed side as:

Effective $AaDO_2$ = effective P_{AO2} – measured P_{aO2} ····· eq. 3

Unless otherwise specified, P_{AO2} and $AaDO_2$ indicate effective P_{AO2} and effective $AaDO_2$, respectively in this review.

Relationships between $AaDO_2$ and V_A/Q distribution decided by MIGET: Differing from the V_A/Q theory developed on the basis of the MIGET, the classical gas-exchange theory is not sufficiently warranted by the anatomical and physiological facts. Hence, it is necessary for certifying the issue of whether the effective P_{AO2} indeed functions as the representative P_{O2} in mixed gas exhaled from all functional gas-exchange units. For answering this question, it is indispensable at least to compare the results obtained from the classical gas-exchange theory with those from the MIGET.

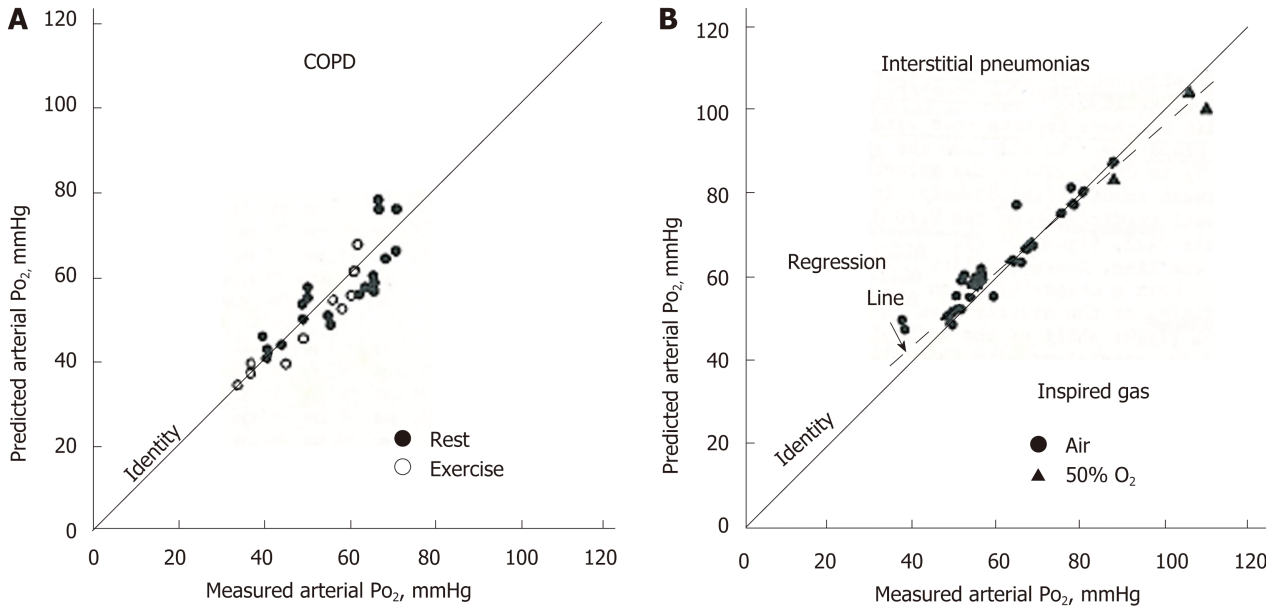


Figure 6 Comparison of predicted P_{aO2} from multiple inert-gas elimination technique and measured P_{aO2}. A: Chronic obstructive pulmonary disease at rest or during exercise; B: Interstitial pneumonias at rest while inspiring gas with 21% O_2 (room air) or 50% O_2. Adopted from ref[76]. COPD: Chronic obstructive pulmonary disease.

We first examined what kinds of V_A/Q units are sensitively detected by O_2. We calculated P_{AO2} in each V_A/Q unit on the assumption that P_{O2} equilibration between alveolar gas and capillary blood is complete (Figure 10). We found that P_{AO2} changes sharply in the units having V_A/Q ranging from 0.1 to 1.0, (*i.e.*, the sensitivity of O_2 to V_A/Q detection is equivalent to that of cyclopropane) but not in other V_A/Q units, suggesting that $AaDO_2$ reflects gas-exchange behavior in regions with moderately low V_A/Q values but is insensitive to gas exchange in regions with very low and high V_A/Q values. The finding indicated that the ability of $AaDO_2$ detecting the V_A/Q heterogeneity was substantially limited and does not cover the whole range of V_A/Q heterogeneity as the MIGET does.

Next, we investigated the coincidence between mixed P_{AO2} estimated from V_A/Q distribution recovered from the MIGET and effective P_{AO2} calculated from eq. 2 in patients with interstitial pneumonia or COPD (Figure 11). The coincidence between the two P_{AO2} was satisfactory, indicating that the effective P_{AO2} and effective $AaDO_2$ can accordingly change reflecting the formation of moderately low V_A/Q regions that is related to the emergence of hypoxemia. Hence, we concluded that effective P_{AO2} and effective $AaDO_2$ are practically useful in a clinical setting as far as the gas-exchange abnormality elicited by moderately low V_A/Q regions is considered.

Pulmonary diffusing capacity for CO (D_{LCO})

General survey on D_{LCO}: The most terminal organization in the lung is alveolocapillary membrane and capillary network embedded in the alveolar wall (septum) (Figure 12). The main mechanism of gas transfer through alveolocapillary membrane and capillary blood is the aqueous-phase diffusion so that the impaired gas transfer there is estimated by measuring the pulmonary diffusing capacity using diffusion-limited gases such as CO and NO, *i.e.*, D_{LCO} and D_{LNO} (Figure 13). About 30 years ago, Guénard *et al*[88] and Borland and Higginbottom[89] independently elaborated a method for measuring the D_{LNO}. NO has an extremely high affinity with Hb, *i.e.*, 400000 times higher than that of O_2 and 1800 times higher than that of CO[65], which indicates that the chemical reaction of NO with Hb has virtually no obstacle to NO uptake by erythrocytes (*i.e.*, diffusion limitation but no reaction limitation). Therefore, the partial pressure of NO in pulmonary capillary network is assumed to be practically zero, suggesting that D_{LNO} may be predominantly decided by the diffusive process across alveolocapillary membrane and erythrocytes. However, this does not hold true in the case of D_{LCO}, in which besides the diffusive process across alveolocapillary membrane and erythrocytes, the replacement reaction of CO with HbO_2 causes a substantial resistance to CO transfer, *i.e.*, diffusion limitation plus reaction limitation. In the current review, we will confine ourselves to describe D_{LCO} only. This is simply because D_{LNO} is not presently measured worldwide. If readers want to know a more comprehensive discussion on D_{LCO} and D_{LNO}, we refer them to a

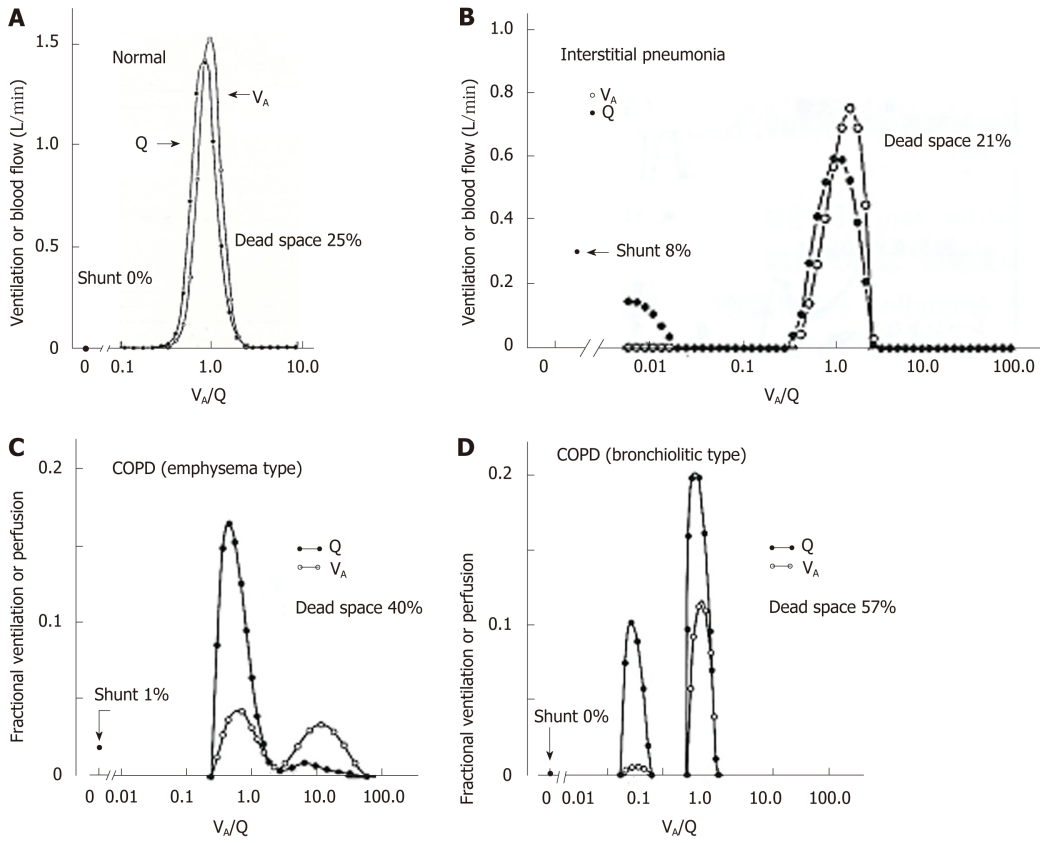


Figure 7 Representative ventilation-perfusion distributions predicted from multiple inert-gas elimination technique in various types of lung diseases. A: Young normal subject; B: Patient with interstitial pneumonia; C: Chronic obstructive pulmonary disease patient with predominant emphysema; D: Chronic obstructive pulmonary disease patient with predominant bronchiolitis. See text for detailed explanation. Adopted from ref[59]. V_A/Q: Ventilation-perfusion; COPD: Chronic obstructive pulmonary disease.

more extensive review reported by us[65].

It has been over 100 years since Krogh[90] developed the method to measure the single-breath CO uptake through alveolocapillary membrane. Since then, the single-breath D_{LCO} has gained a position as the most clinically useful pulmonary function test after spirometry and lung volume examination. The practical method to examine the single-breath D_{LCO} was proposed by Ogilvie *et al*[91]. Concurrently, Roughton *et al*[92] proposed an important model describing the gas transfer through alveolocapillary membrane and erythrocytes. They assumed that the CO transfer process from alveolocapillary membrane to Hb condensed within erythrocytes could be simplified into the two processes; *i.e.*, (1) the membrane diffusing capacity for CO (D_{MCO}) that reflects the diffusion limitation across alveolocapillary membrane and plasma layer surrounding erythrocytes, and (2) the blood diffusing capacity for CO (D_{BCO}) that is defined as the product of capillary blood volume (V_C) and specific gas conductance for CO in the blood (θ_{CO}). The θ_{CO} signifies the diffusive process across erythrocyte membrane and its interior incorporated with the competitive replacement reaction of CO with HbO_2. Since the reciprocals of D_{MCO} and D_{BCO} are the gas-transfer resistances that are connected in series, the total resistance for CO transfer, $1/D_{LCO}$, is expressed as

$$1/D_{LCO} = 1/D_{MCO} + 1/(\theta_{CO} \cdot V_C) \cdots\cdots \text{eq. 4}$$

In addition to the D_{LCO}, the D_{LCO}/V_{AV}, in which V_{AV} denotes the alveolar volume during a single-breath maneuver, is similarly important. This parameter expresses the D_{LCO} per unit alveolar volume, which is equal to the Krogh factor (K_{CO}), *i.e.*, the rate constant of alveolar gas uptake per unit pressure. The relative contribution of $1/D_{MCO}$ and that of $1/D_{BCO}$ to overall resistance of CO transfer ($1/D_{LCO}$) were found to be 23% and 77%, respectively (Figure 14)[65,93]. The finding indicated that D_{LCO} is primarily weighted by D_{BCO}, suggesting that D_{LCO}-associated parameters are more susceptible to the damage of pulmonary microcirculation than that of alveolocapillary membrane.

Factors affecting D_{LCO} and K_{CO}: The D_{LCO} and K_{CO} are the physiological parameters that are useful for diagnosing the pathological changes occurring in alveolocapillary membrane and pulmonary microcirculation. However, there are many matters that

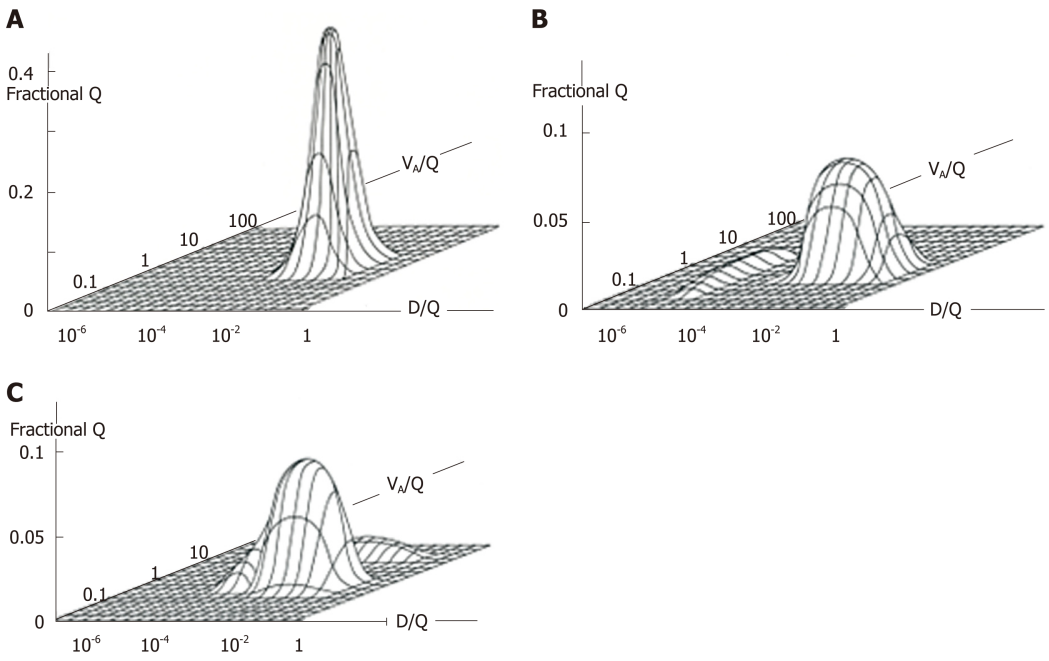


Figure 8 Ventilation-perfusion (V_A/Q)-Diffusing capacity-perfusion (D/Q) distributions in normal and diseased lungs. A: V_A/Q and D/Q distribution in normal lung; B: That in lung with desquamative interstitial pneumonia; C: That in lung with chronic obstructive pulmonary disease characterized by emphysema. Patient with desquamative interstitial pneumonia (B) revealed minimal V_A/Q heterogeneity but very low D/Q regions that may yield "diffusion shunt" contributing to hypoxemia. Very low D/Q regions may be caused by decreased surface area and/or increased thickness of alveolocapillary membrane. Patient with chronic obstructive pulmonary disease (C) showed V_A/Q heterogeneity with high V_A/Q regions but minimal regions with very low D/Q. Modified from ref[80].

should be argued with regard to the D_{LCO}-related parameters as listed below.

Influence of back-pressure of CO from pulmonary capillary blood: The CO back-pressure during D_{LCO} measurement is estimated at about 3% of the alveolar P_{CO} in a nonsmoking subject[65]. Therefore, the effect of CO back-pressure on D_{LCO} can be ignored in a subject with no habitual smoking. However, heavy smokers or repeated measurements of D_{LCO} produced the CO back-pressure that is not disregarded because the CO back-pressure reaches about 16% of the alveolar P_{CO}, which induces a significant error while estimating the overall D_{LCO}.

Influence of functional heterogeneities: The D_{LCO} is influenced by at least three heterogeneities[65]; (1) the distribution of alveolar tidal volume to alveolar volume (V_{AT}/V_{AV}), (2) that of diffusing capacity to alveolar volume (D_{LCO}/V_{AV}, *i.e.*, K_{CO}), and (3) that of alveolar tidal volume in each region to total alveolar tidal volume. Of these, the heterogeneity of K_{CO}, which may be caused by the regional difference in rate constant of CO uptake due to local variations in the thickness of alveolocapillary membrane and plasma layer as well as the density of erythrocytes in microcirculation[94], is the most important, while other two heterogeneities may be considerably degraded during a breath-holding maneuver. Piiper and Sikand[95,96] theoretically and experimentally analyzed the significance of K_{CO} heterogeneity on overall D_{LCO}, resulting in a larger D_{LCO} value for a shorter breath-hold time. Furthermore, their analysis[95,96] identified that the overall D_{LCO} may be underestimated by 37% in a condition where a serious K_{CO} heterogeneity exists. However, it is impossible to universally apply the value reported by Piiper and Sikand[95,96] to clinical cases having various types of lung diseases because the extent of K_{CO} heterogeneity differs substantially in respective patients. Therefore, the measured D_{LCO} should be regarded as the "apparent or effective" value that is always underestimated by the K_{CO} heterogeneity to an uncertain extent.

To note, if the diffusing capacity (D) for a certain gas is measured under a steady-state condition, the apparent D value is significantly reduced due to the V_A/Q and D/Q heterogeneities. Indeed, Yamaguchi *et al*[80] identified an appreciable effect of these heterogeneities on apparent D value, particularly in patients with interstitial lung diseases (Figure 8).

Influence of alveolar volume: Declining alveolar volume (V_{AV}) without loss of acini (for instance, inspiratory muscle insufficiency) accompanies[65,97]: (1) slight decrease in D_{MCO}/V_{AV} but large increase in V_C/V_{AV}, (2) decrease in D_{LCO}, and (3) increase in K_{CO}, which indicates the "facilitated" CO transfer per unit lung volume in conditions with declining V_{AV} with no loss of acini. Overall V_C remains constant due to the stability of

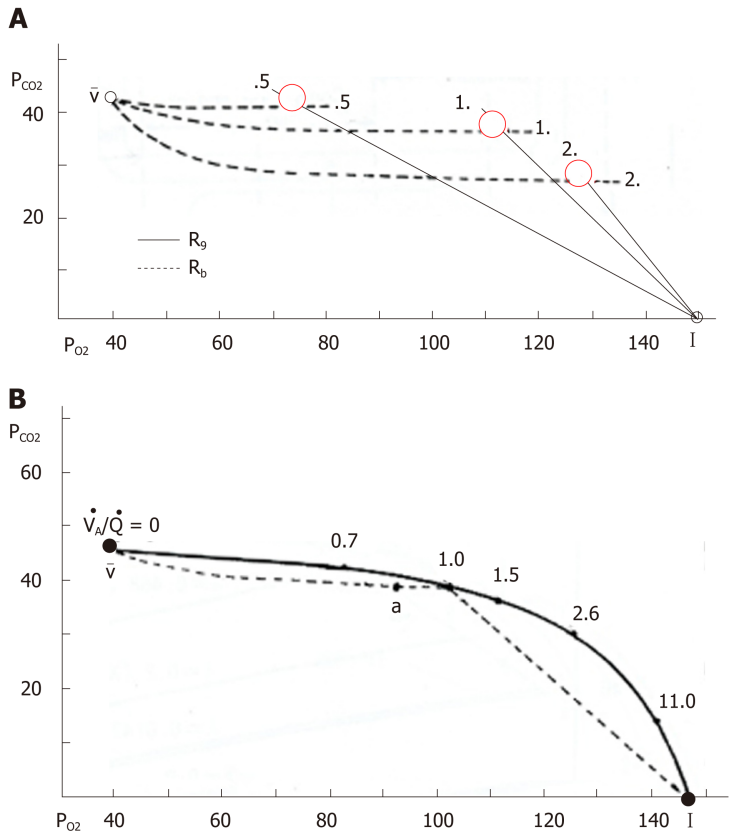


Figure 9 O_2-CO_2 diagram and ventilation-perfusion line. A: O_2-CO_2 diagram, in which solid and dotted lines indicate gas R lines and blood R lines, respectively. Intersection of these two lines denoted by red circle provides a single ventilation-perfusion value and corresponding unique pair of P_{O2} and P_{CO2}; B: Ventilation-perfusion line constructed by connecting each intersection of gas R lines and blood R lines. I: Inspired point; a: Arterial point; v: Mixed venous point. See text for further explanation. Adopted from ref[87].

cardiac output (Q), which reinforces the redistribution of pulmonary perfusion during lung volume changes; thus V_C/V_{AV} increases with decreasing V_{AV}. Reduced V_{AV} decreases D_{MCO} but does not change V_C, leading to decreased D_{LCO}. Hence, the characteristic of decreased V_{AV} without loss of acini is decreased D_{LCO} in association with increased K_{CO}.

The situation is different in the diminished expansion caused by loss of acini such as post-pnemonectomy. Declining V_{AV} with losing acini elicits[65,97]: (1) decrease in both D_M and V_C associated with large decrease in D_{LCO}, (2) small increase in V_C/V_{AV} accompanied with increased D_{MCO}/V_{AV} (this is attributed to the redistribution of Q), and (3) small change in K_{CO}. The trend of D_{MCO}/V_{AV} is opposite to that without loss of acini. The extent of increased V_C/V_{AV} in lungs with loss of acini is less than that without loss of acini, leading to a restricted increase in K_{CO} (*i.e.*, a lesser improvement of CO uptake per unit lung volume) in lungs with losing acini.

Influence of cardiac output: The increased Q (for instance, left-to-right shunt) elicits capillary distension and/or recruitment, leading to the increased surface area of alveolocapillary membrane (rise in D_{MCO} and D_{MCO}/V_{AV}) and the augmented capillary blood volume (rise in V_C and V_C/V_{AV}), which increase both D_{LCO} and K_{CO}. On the other hand, decreased Q shows the opposite trend[98,99].

Influence of alveolar hemorrhage: The behaviors of D_{LCO} and K_{CO} in patients with alveolar hemorrhage (for instance, ANCA-associated microscopic polyangiitis) are qualitatively similar to those observed in patients with increased Q. This is because hemorrhage-derived Hb released into the alveolar space absorbs CO before it reaches the capillary blood such that both D_{LCO} and K_{CO} are elevated even under a condition where alveolar walls are significantly injured.

Differential diagnosis based on behaviors of D_{LCO} and K_{CO}: The decrease in both D_{LCO} and K_{CO} is the general feature in lungs with various injuries of alveolocapillary membrane and/or pulmonary microcirculation because they reduce D_{MCO}, D_{BCO}, or both. We want to define these general behaviors of D_{LCO} and K_{CO} as the type-1 abnormality. However, there are many pathological conditions that do not follow the

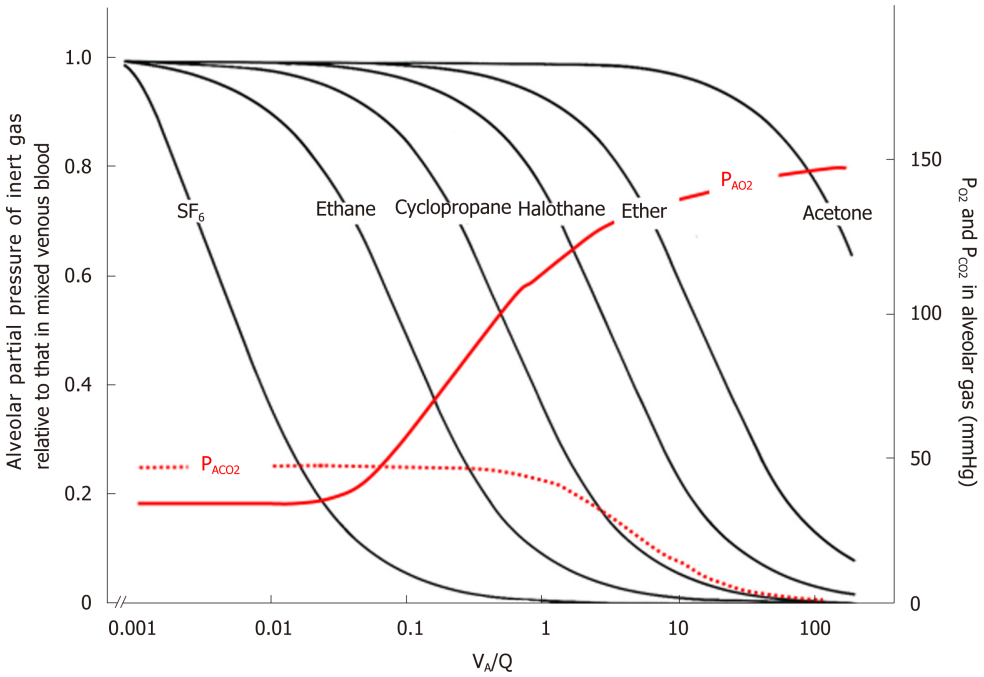


Figure 10 Ventilation-perfusion (V_A/Q) regions detected from gas exchange behaviors of O_2, CO_2, and inert gases. Left ordinate: excretion (E) of inert gas defined as P_A/P_v, where P_A is partial pressure of inert gas in each functional gas-exchange unit, while P_v is that in mixed venous blood. Right ordinate: P_{AO2} and P_{ACO2} in each functional gas-exchange unit. Abscissa: logarithmic V_A/Q value. E of each inert gas sharply changes in a certain range of V_A/Q depending on its blood-gas partition coefficient (λ). For instance, sharp change in E for SF_6 is found at V_A/Q ranging between 0.001 and 0.01. As such, SF_6 has high sensitivity to detecting gas exchange in regions with very low V_A/Q. On the other hand, E for acetone sharply changes at V_A/Q ranging from 10 to 100, indicating that acetone is susceptible to gas exchange in regions with very high V_A/Q. P_{AO2} changes greatly at V_A/Q ranging between 0.1 and 1.0, suggesting that O_2 has sensitivity to detecting gas exchange in regions with moderately low V_A/Q (like cyclopropane). Meanwhile, CO_2 is susceptible to gas exchange in regions with moderately high V_A/Q ranging from 1.0 to 10 (like halothane).

principle of type-1 abnormality. As discussed above, declining alveolar volume without loss of acini leads to decreased D_{LCO} in association with increased K_{CO}. We define these behaviors of D_{LCO} and K_{CO} as the type-2 abnormality. On the other hand, declining alveolar volume with losing acini elicits decreased D_{LCO} and restricted rise in K_{CO}. We define these aspects of D_{LCO} and K_{CO} as the type-3 abnormality. Increased Q and alveolar hemorrhage increase both D_{LCO} and K_{CO}. We define these increasing aspects of D_{LCO} and K_{CO} as the type-4 abnormality.

In 1951, Austrian *et al*[100] first proposed the disease concept of "alveolar-capillary (A-C) block." This classic syndrome originated to describe the interference of gas transfer through alveolocapillary membrane by aqueous-phase diffusion in patients with various kinds of interstitial lung disease[101,102]. However, many physiologists and clinicians have questioned the role of impaired aqueous-phase diffusion as the factor inducing hypoxemia. This is because in addition to alveolar interstitium, acinar airways and pulmonary microcirculation are simultaneously injured in most of the interstitial lung diseases. The impediment of acinar airways and/or microcirculation evokes the V_A/Q heterogeneity leading to hypoxemia. In relation to this problem, there has been no direct study credibly addressing the issue of whether the impaired aqueous-phase diffusion across alveolocapillary membrane can indeed evoke hypoxemia. To answer this question, all gas-exchange parameters, including V_A/Q distribution, $AaDO_2$, D_{LCO}, and K_{CO}, should be simultaneously examined in patients with pathologically-confirmed pure lesion of impaired alveolocapillary membrane but no lesion of acinar airways or pulmonary microcirculation.

CONCLUSION

To answer the questions that have remained unsolved in the field of respiratory physiology, we analyzed the structure-function relationships in the lung from a variety of anatomical and physiological points of view. The important results found therefrom are as follows: (1) The model A of Weibel is useful for estimating gas mixing in peripheral conducting airways; (2) The anatomical gas-exchange unit is organized by the acinus of Loeschcke; (3) Although it is difficult to define the functional gas-exchange unit correctly, the acinus of Aschoff may act as the functional

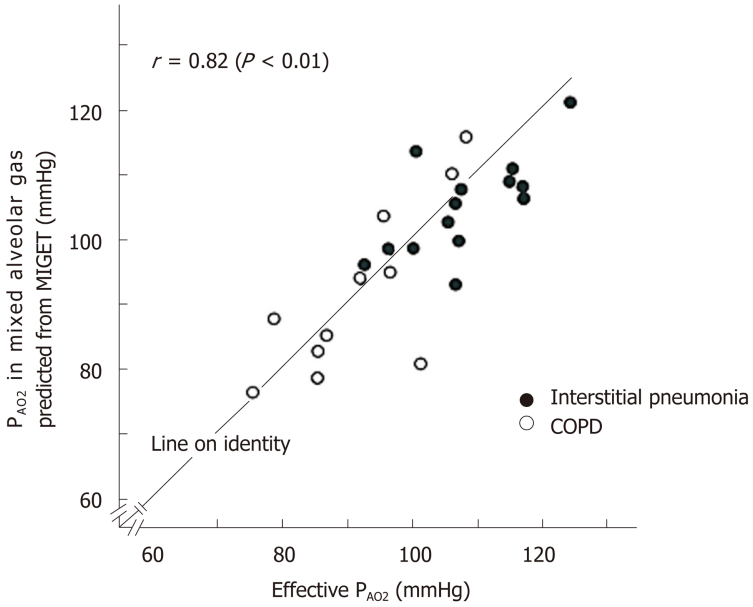


Figure 11 Comparison of effective P_{AO2} and P_{AO2} in mixed alveolar gas estimated from ventilation-perfusion distribution decided by multiple inert-gas elimination technique. Effective P_{AO2} and P_{AO2} estimated from multiple inert-gas elimination technique were compared [patients with interstitial pneumonia (*n* = 14) and chronic obstructive pulmonary disease (*n* = 11)]. Coincidence of two P_{AO2} is satisfactory. See text for further explanation.

gas-exchange unit in an initial approximation; (4) The MIGET is supported by the anatomical and physiological backgrounds in many respects. Therefore, the MIGET is clinically valuable for predicting the heterogeneous V_A/Q distribution between the acini of Aschoff under steady-state conditions; (5) The effective $AaDO_2$ sensitively detects moderately low V_A/Q regions causing hypoxemia. Hence, the $AaDO_2$ is taken as a useful, clinical indicator for predicting impaired gas exchange. However, one should be aware that the $AaDO_2$ is insensitive to impaired gas exchange caused by very low V_A/Q regions and/or high V_A/Q regions; (6) The D_{LCO} and K_{CO} (D_{LCO}/V_{AV}) are useful for diagnosing the impediment of alveolar walls, including alveolocapillary membrane and pulmonary microcirculation. However, one should recognize the fact that the effect of regional variations in K_{CO} on overall D_{LCO} could not be totally eliminated; and (7) The clinically useful categorization with regard to behaviors of D_{LCO} and K_{CO} is the type-1 abnormality (decrease in both D_{LCO} and K_{CO}), the type-2 abnormality (decrease in D_{LCO} but increase in K_{CO}), the type-3 abnormality (decrease in D_{LCO} but restricted rise in K_{CO}), or the type-4 abnormality (increase in both D_{LCO} and K_{CO}). These categories of D_{LCO} and K_{CO} abnormalities allow for precise differential diagnosis concerning the damage in alveolocapillary membrane and that in pulmonary microcirculation.

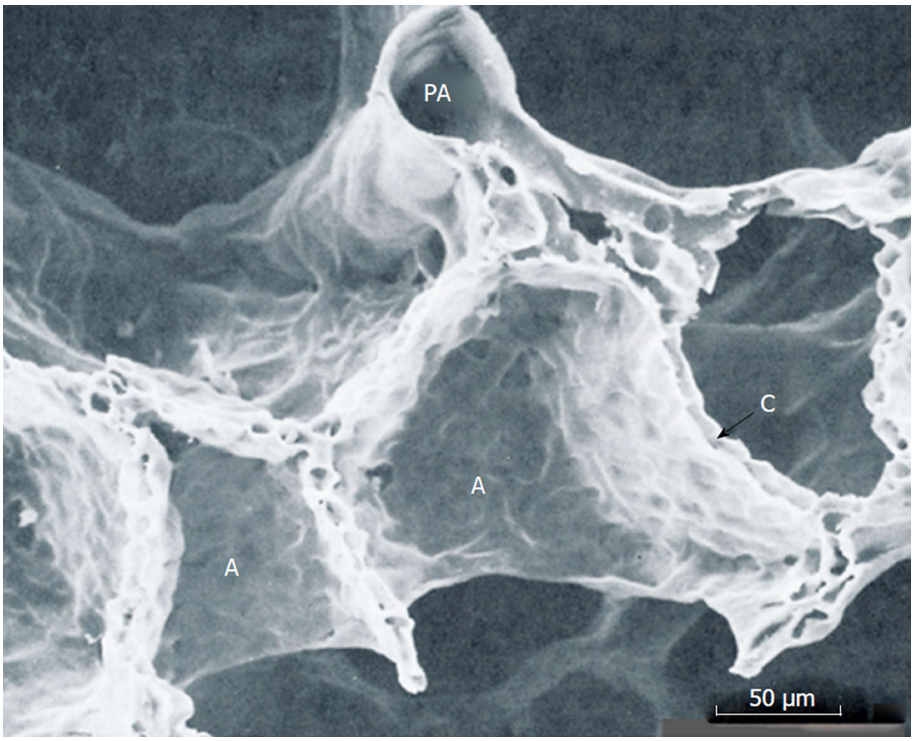


Figure 12 Scanning electron microscopic image of perfusion-fixed alveolar walls. PA: Pulmonary arteriole; A: Alveolar walls, C: Capillary networks embedded in alveolar wall. Adopted from ref[25].

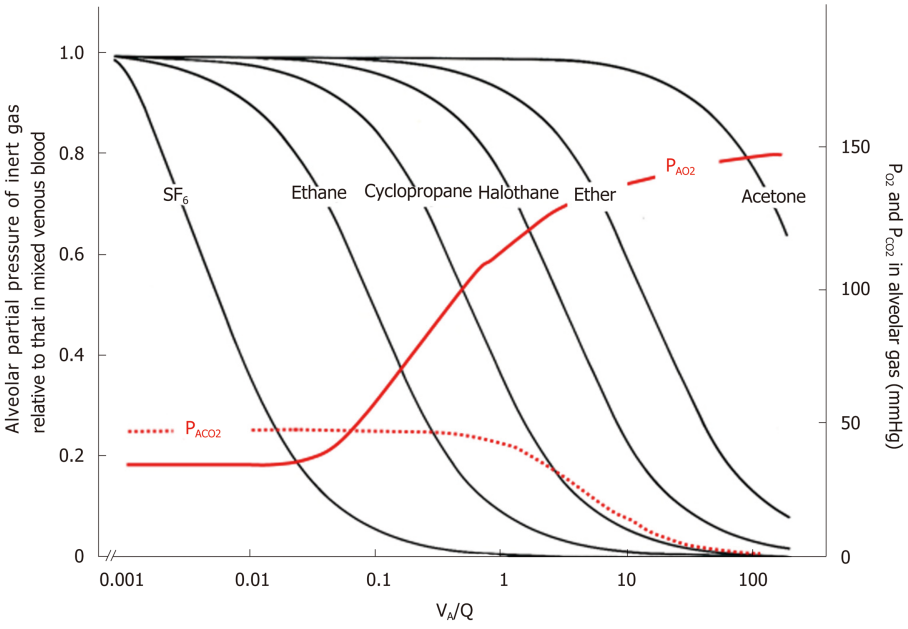


Figure 13 Partial-pressure equilibration of gases between alveolar gas and capillary blood. Inert gases that are not combined with erythrocyte hemoglobin (Hb) show instantaneous equilibration between alveolar gas and capillary blood. O_2 and CO_2 that have relatively low affinity with Hb need some time for completing equilibration between alveolar gas and capillary blood. CO and NO (red lines) that have very high affinity with Hb prevent rise in their partial pressures in capillary blood. Hence, CO and NO do not reach partial-pressure equilibration between alveolar gas and capillary blood any more even in normal lung. Affinity of NO with Hb is extremely high and chemical reaction of NO with Hb is very rapid such that partial pressure of NO in capillary blood is maintained at negligible level. Therefore, there is no "back-pressure" effect during measurement of D_{LNO}. However, affinity of CO with Hb is lower than that of NO (*i.e.*, 1/1800 times that of NO). Therefore, partial pressure of CO in capillary blood rises gradually such that "back-pressure" of CO from capillary blood should not be ignored while measuring the pulmonary diffusing capacity for CO.

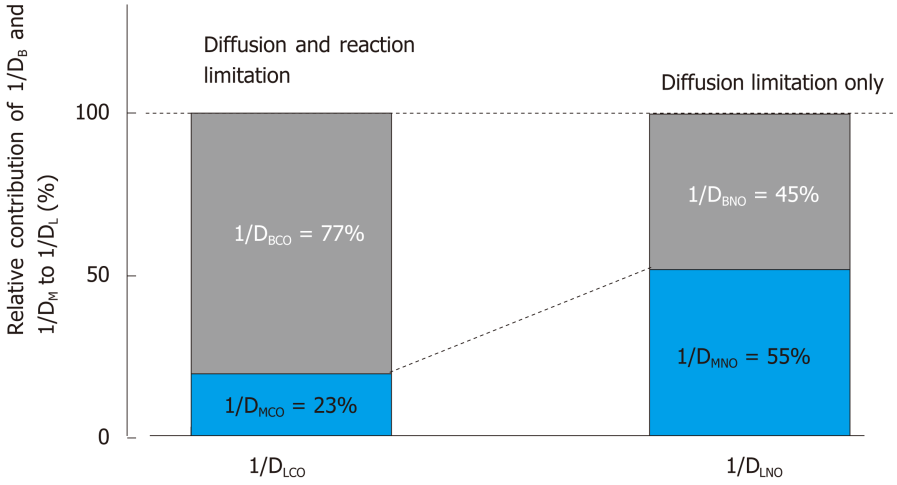


Figure 14 Relative contribution of $1/D_M$ and $1/D_B$ to overall resistance of $1/D_L$. Difference in membrane diffusing capacity for CO (D_{MCO}) and that for NO (D_{MNO}) is simply attributed to difference in their Krogh diffusion constants defined as (α·d), where α is Bunsen solubility coefficient of the gas (mL/mL/atm) and d is gas diffusivity (cm^2/s) in alveolocapillary membrane and plasma layer. D_{MNO}/D_{MCO} is assumed to be 1.97[65]. On the other hand, blood-diffusing capacity for CO (D_{BCO}) or NO (D_{BNO}) is defined as alveolar capillary blood volume (V_C) multiplied by specific gas conductance of each gas (θ_{CO}, θ_{NO}). θ_{CO} signifies the diffusive process across erythrocyte membrane and its interior incorporated with the competitive, replacement reaction of CO with hemoglobin O_2. Therefore, θ_{CO} changes significantly depending on surrounding P_{O2}. On the other hand, θ_{NO} is not influence by chemical reaction with hemoglobin and is predominant by diffusion across erythrocytes, thus resulting in constant θ_{NO} [4.5 mL/min/mmHg/(mL×blood)[65,93]]. The pulmonary diffusing capacity for CO is primarily governed by both diffusion through alveolocapillary membrane and erythrocytes as well as reaction in erythrocytes (limitation by both diffusion and reaction), whereas the pulmonary diffusing capacity for NO is almost evenly prescribed by diffusion through alveolocapillary membrane and that inside erythrocytes (diffusion limitation only). Important message drawn from this analysis is that the pulmonary diffusing capacity for NO is evenly sensitive to morphological abnormality in alveolocapillary membrane as well as that in pulmonary microcirculation. On the other hand, the pulmonary diffusing capacity for CO is more sensitive to microcirculatory abnormality. Adopted from ref[65].

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EDITORIAL

Diagnosis and treatment of subsegmental pulmonary embolism

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Abstract

Subsegmental pulmonary embolism (SSPE) affects the 4th division and more distal pulmonary arterial branches. SSPE can be isolated or affect multiple subsegments, be symptomatic or incidental (unsuspected) and may or may not be associated with deep vein thrombosis. Symptoms, clinical risk scores and biomarkers are less sensitive for diagnosing SSPE compared to more central pulmonary embolism. The diagnosis is confirmed using radiological imaging, predominately computed tomographic pulmonary angiogram (CTPA) or ventilation/perfusion scanning. The increasing utilization of CTPAs may have resulted in overdiagnosis driven by smaller pulmonary emboli. There is insufficient evidence of improved mortality or reduced venous thromboembolism recurrence with anticoagulation treatment for SSPE however, the major and clinically significant haemorrhage risks are well described. As the resolution of diagnostic imaging has improved, we may be viewing the natural physiological filtering process performed by the lungs that may not require treatment.

Key words: Subsegmental pulmonary embolism; Venous thromboembolism; Incidence; Diagnosis; Treatment

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Core tip: Current guidelines suggest that isolated subsegmental pulmonary embolism (SSPE) patients at low risk of venous thromboembolism (VTE) recurrence and without concurrent proximal VTE can be followed up with clinical surveillance in preference to anticoagulation. This is based on limited evidence and a randomised controlled trial is required to determine the risks and benefits of anticoagulation in SSPE.

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INTRODUCTION

Subsegmental pulmonary embolism (SSPE) affects the 4th division and more distal pulmonary arterial branches. Additional SSPE classification varies throughout the literature and standardisation has remained a challenge. SSPE can be isolated or affect multiple subsegments, be symptomatic or incidental (unsuspected) and may or may not be associated with deep vein thrombosis (DVT). Incidental SSPE occurs when imaging is performed for alterative reasons predominately cancer staging, trauma and post-operative evaluation[1]. The classification and subtyping of SSPE is compounded by the complexities surrounding diagnosis.

The most common symptom in SSPE is chest pain, compared to breathlessness in more central pulmonary embolism[2]. Interestingly, even apparently asymptomatic patients with incidental pulmonary embolism (IPE) may have suggestive symptoms on closer review[3]. The smaller embolic burden in SSPE is associated with less hypoxia, less haemodynamic instability, lower plasma D-dimer, N-terminal pro b-type natriuretic peptide (NT-proBNP), troponin and less concurrent proximal DVT[2,4,5]. Consequently, pre-test clinical prediction rules for pulmonary embolism (*e.g.*, the Wells score) are less sensitive in SSPE[6,7]. As symptoms, clinical risk scores and biomarkers are less sensitive, SSPE is confirmed using radiological imaging, predominately computed tomographic pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scanning. Modern CTPA is used widely to diagnose pulmonary embolism due to its availability, sensitivity and ability to detect additional and alternative findings. The utilization of CTPAs increased 14-fold between 2001 and 2008, whilst V/Q decreased by 52% during the same time period[8]. SSPEs can be challenging to diagnose on CTPA and this is reflected by the intra-observer reliability being lower than for more proximal pulmonary embolisms. In a retrospective series, when a panel of expert thoracic radiologists reviewed the diagnosis of SSPE, 59% were considered false positives[9]. This occurs due to technical factors including breathing motion and beam hardening artifact along with the specialization and experience of the reporting radiologist[9].

Currently, there are no known differences in the aetiology or pathobiological mechanisms between SSPE and more central pulmonary embolism. Furthermore, it is unclear from the current literature whether some isolated SSPE (without the presence of DVT) may represent thrombosis in situ within the pulmonary arteries.

The incidence of pulmonary embolism increased dramatically after the widespread introduction of CTPA. In a United States study, there was an 81% increase (from 62 to 112 cases per 100000) between 1998 and 2006 that coincided with their introduction[10]. The increased pulmonary embolism incidence has been partially attributed to the increased detection of smaller PEs including SSPE[8]. The proportion of pulmonary embolisms that are subsegmental has increased from 4.7% (95%CI: 2.5%-7.6%) with single detector CTPAs to 15.0% (95%CI: 7.7%-24.1%) with 64-slice multi-detector CTPAs[11]. A 2018 systematic review and meta-analysis of 14 studies by Bariteau *et al*[12] reported a more modest pooled prevalence for SSPE as 4.6% (95%CI: 1.8%-8.5%) of all pulmonary embolisms. The incidence of IPE in cancer is 1%-5%, and the proportion that are SSPEs is 8.5%[13]. However, a comparison with the incidence of symptomatic SSPE is difficult as the diagnosis of IPE frequently occurs using contrast enhanced CT rather than formal CTPA[13].

A 2016 Cochrane review concluded that there were no randomised controlled trials to guide the effectiveness of anticoagulation treatment for isolated or incidental SSPE[14]. In 2014, the European Society of Cardiologists (ESC) pulmonary embolism guidelines proposed individualised risk assessment to guide the need for anticoagulation in isolated SSPE[15]. This approach was extended by the recent 2016 American College of Chest Physicians (ACCP) guidelines, that advocates clinical surveillance for SSPE without proximal DVT and with a low risk of recurrence in preference to anticoagulation[16]. Therefore, low risk isolated SSPE without concurrent DVT may not require treatment with anticoagulation. However, this was deemed a weak recommendation based on low quality evidence highlighting the urgent need for trials to address this area[16]. In practice, international physician surveys have highlighted that the majority of SSPEs are treated with anticoagulation due to uncertainty about the natural history of the disease and consequences of not treating[17]. Anticoagulation is not without risks and is associated with bleeding in 8.1% (95%CI: 2.8%-15.8%) of patients with SSPE[12]. The bleeding risks in SSPE patients that do not receive anticoagulation are unknown however, in other cohorts of untreated venous thromboembolism (VTE) patients, the major bleeding rates are 0.6% per patient year[18]. Bleeding definitions vary across SSPE studies and thus are difficult to compare with other pulmonary embolism distributions and overall pulmonary embolism bleeding rates. In a meta-analysis by van der Hulle *et al*[19] of VTE patients treated with direct oral anticoagulants (DOACs)(n = 12153), 1% of patients had major

bleeding and 6.6% had clinically relevant non-major bleeding when standardised definitions were applied.

The outcomes following SSPE have predominately focused on VTE recurrence, bleeding complications and mortality. In the Bariteau *et al*[12] meta-analysis, VTE reoccurred in 5.3% (95%CI: 1.6%-10.9%) of anticoagulation treated SSPE patients (n = 589) compared with 3.9% (95%CI: 4.8%-13.4%) of untreated patients (n = 126) within 90 d. This may be an overestimate, as there was only a 2% VTE recurrence rate for DOAC treated VTE in the van der Hulle *et al*[19] meta-analysis[19]. A higher D-dimer and concurrent proximal DVT are both associated with increased mortality in pulmonary embolism[20,21]. As D-dimer is lower in SSPE and proximal DVT less frequent, we may expect to see more favorable survival in SSPE compared to more central pulmonary embolism[22]. Whilst some studies have reported higher mortality in central pulmonary embolisms compared with more distal, others have suggested survival in SSPE is no different[6,21]. In the Bariteau *et al*[12] meta-analysis, all-cause mortality occurred in 2.1% (95%CI: 0.3%-5.2%) of anticoagulation treated SSPE patients and 3.0% (95%CI: 2.8%-8.6%) of untreated patients. This compares to 2.4% in the DOAC treated VTE meta-analysis, however, the SSPE meta-analysis analysis was limited by a preponderance of retrospective studies and significant heterogeneity between studies[12,19]. Additional SSPE outcomes including qualitative risk/benefit assessment, patient reported outcomes, health utilization and health economic analyses remain to be fully explored.

Interestingly, the case fatality rate (proportion of people with PE that die from it) decreased by one third (from 12.1% to 7.8%) after the introduction of CTPAs, whilst overall pulmonary embolism mortality stayed reasonably static (from 12.3 to 11.9 per 100000) in a United States study[10]. The increasing incidence of pulmonary embolism together with decreased case fatality and minimal mortality change has raised concerns about overdiagnosis, driven by the diagnosis of smaller pulmonary embolisms[8]. In a randomised non-inferiority trial, pulmonary embolism was identified in a significantly higher number of CTPAs than VQ scans (19.2% *vs* 14.2%)[23]. There was no difference in symptomatic VTE recurrence (0.4% *vs* 1.0%) or mortality between the two cohorts, suggesting that the additionally diagnosed pulmonary embolisms in the CTPA group may not be clinically relevant[23].

There remain several unanswered questions regarding the optimal diagnosis and management of SSPE. The poor intra-observer reliability of SSPE using CTPA could be improved with computer aided diagnosis[24]. Image recognition and machine learning could also help standardise the radiological classification of pulmonary embolism for research trials. Whilst pulmonary embolism is often categorised into discrete anatomical subtypes (*e.g.*, segmental, subsegmental) the pulmonary vasculature is a continuous structure. Improved radiological phenotyping would enable diagnostic standardisation and identification of varied outcomes with graduated and precise phenotypes. Secondly, there is currently insufficient evidence for the optimal treatment of SPPE. Most studies exploring the management of SSPE have been single-centre, retrospective and lack robust outcome definitions particularly relating to the risks of bleeding. Consequently, meta-analysis and systematic reviews of SSPEs are limited by significant heterogeneity between studies[12]. These limitations should be addressed with a randomised controlled trial (RCT) of anticoagulation *vs* no treatment for SSPE. Important contributors to SSPE outcomes including the complexity of radiological diagnosis and classification, false positives, intra-observer reliability, concomitant DVT and cancer could be investigated and controlled for within an RCT.

CONCLUSION

The increasing utilization of CTPAs may have resulted in overdiagnosis driven by smaller pulmonary emboli. There is insufficient evidence of improved mortality or reduced VTE recurrence with anticoagulation treatment for SSPE however, the major and clinically significant haemorrhage risks are well described. As the resolution of diagnostic imaging has improved, we may be viewing smaller pulmonary emboli that do not require treatment. We are overdue a randomized controlled trial of anticoagulation in SSPE to establish the risks and benefits of treatment. Just because we can anticoagulate patients with SSPE, it doesn't mean that we should.

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