

Pattern of total and regional lung function in subjects with bronchoconstriction induced by 15-me PGF_{2α}¹

L. HESLET ANDERSEN and N. J. SECHER

Departments of Clinical Physiology and Gynaecology and Obstetrics, Odense University Hospital, DK-5000 Odense, Denmark

Andersen, L. H. and Secher, N. J. (1976). *Thorax*, 31, 685–692. **Pattern of total and regional lung function in subjects with bronchoconstriction induced by 15-me PGF_{2α}.** Closing volume (single breath nitrogen test), regional ventilation and perfusion (using intravenous xenon-133), and total lung function (TLC, VC, and FEV₁) were measured before and after intramuscular administration of 250 μg 15-methyl prostaglandin F_{2α} (15-me PGF_{2α}) in 10 healthy women. The cardiac output was measured with the Minnesota impedance cardiograph model 304A and the transthoracic impedance was used as an expression of the thoracic fluid volume. The slope of the alveolar plateau on the closing volume tracing showed a 271 % increase 20 minutes after the prostaglandin administration, at which time the closing volume per cent (CV %) had decreased ($P < 0.01$) and the closing capacity (CC %) had increased ($P < 0.05$). Vital capacity (VC) decreased ($P < 0.01$), residual volume (RV) increased ($P < 0.01$), and the total lung capacity (TLC) remained unchanged. The maximal decrease (9 %) in FEV₁ was seen after 20 minutes. All these measurements except the slope of the alveolar plateau returned to control levels after 60 minutes. The redistribution of regional ventilation was more pronounced than that of the regional pulmonary blood flow. No change was observed in cardiac output and transthoracic impedance. None of the patients experienced any dyspnoea. Our results are consistent with a more pronounced effect of prostaglandin F_{2α} on the small airways (the alveolar plateau) than on the larger airways (FEV₁). In cases where an increase in the slope of the alveolar plateau is observed, the closing volume per cent should not be used as a measurement of the lung disease. It is concluded that the single breath nitrogen test (N₂ closing volume) is more sensitive than the conventional tests.

The prostaglandins (PG) have been shown to produce a pronounced effect on the pulmonary circulation in animal studies (Alpert *et al.*, 1973; Kadowitz, Joiner, and Hyman, 1974). Pronounced bronchoconstrictive effect has been seen in human studies after administration of prostaglandin F_{2α} (PGF_{2α}) (Smith, 1973). Various stimuli have been shown to release prostaglandin from lung tissue (Shaw and Moser, 1975) and it has been suggested that the local release of prostaglandins may influence the ventilation/perfusion ratio (Piper and Vane, 1971). The purpose of the present investigation was to study the sensitivity and changes in the single breath nitrogen test measurements (slope of phase III, closing volume per

cent (CV %), and closing capacity (CC %)) and the conventional static and dynamic spirometric tests after the administration of PGF_{2α}. Radiospirometry by intravenous administration of xenon-133 (¹³³Xe) was performed for further evaluation of the changes induced by the 15-methyl derivative of PGF_{2α} (15-me PGF_{2α}).

Prostaglandins are being widely used for induction of labour and abortion. For this reason it is important to evaluate the effect of 15-me PGF_{2α} on the pulmonary circulation and ventilation in humans, as these agents may be contraindicated in patients with cardiopulmonary diseases.

MATERIAL AND METHODS

The aim of the present study, the experimental

¹ A part of this study was presented at the Symposium on Closing Volume, Odense, Denmark, 20–21 October 1975

procedure, and possible side effects of the drug were explained in detail to the subjects, aged 22–36 years. Thereafter the 10 subjects consented to take part in the investigation. There was no history or physical sign of cardiopulmonary abnormality in any of these subjects, neither was any of them a heavy smoker (< 10 cigarettes per day).

Closing volume was measured by the single breath nitrogen test modified by Mansell, Bryan, and Levison (1972), Oxhøj and Bake (1974), and carefully described by Rasmussen, Sølvsteen, and Andersen (1975). The measuring system consists of a 'bag in box' system, a nitrogen analyser with remote measuring head (Godart Nitrograph type 18121), and a water-sealed spirometer fitted with an analogue potentiometer, the output of which (volume (X-axis)) was registered versus the output from the nitrogen analyser (nitrogen per cent (Y-axis)) on an XY-recorder (Hewlett-Packard 7054A). The apparatus had a dead space of 150 ml and external resistances in the inspiratory and the expiratory tubing in order to limit the inspiratory and expiratory flow rates to less than 0.5 litres per second. When the subject is seated and fitted with a mouthpiece and noseclamp, the system is operated by five solenoid valves directing the respiratory flow. The subject exhales maximally to the atmosphere, signals the operator, and is switched on to the apparatus, after which maximal

inspiration is carried out immediately followed (without breath-holding) by a maximal expiration. An interval of 5 minutes is interposed in order to restore alveolar nitrogen concentration (F_{AN_2}). Nitrogen concentration versus volume are registered during both inspiration and expiration; this gives a typical tracing (Fig. 1, control level). It is possible in this way to register endexpiratory alveolar nitrogen concentration (F_{AN_2}) and both inspiratory and expiratory vital capacity (VC_i and VC_e), thus ensuring the delivery of the nitrogen bolus near residual volume (RV). The slope of the best fitting line (slope III) drawn through the largest possible part of the alveolar plateau (phase III) represents the degree of uneven alveolar ventilation (Buist and Ross, 1973b). The place at which the tracing finally departs from this line is believed to represent the onset of airway closure and is named the closing point. The expired volume from this point until the end of the tracing is named closing volume or phase IV.

The only tracings accepted were within the range:

$$-10\% \leq (VC_i - VC_e) \times 100 / VC \leq +5\%$$

where VC is the largest of VC_i and VC_e . Closing volume was expressed as:

$$(a) CV\% = \text{phase IV} \times 100 / VC$$

and

$$(b) CC\% = (\text{phase IV (BTPS)} + RV \text{ (BTPS)}) \times 100 / TLC \text{ (BTPS)}$$

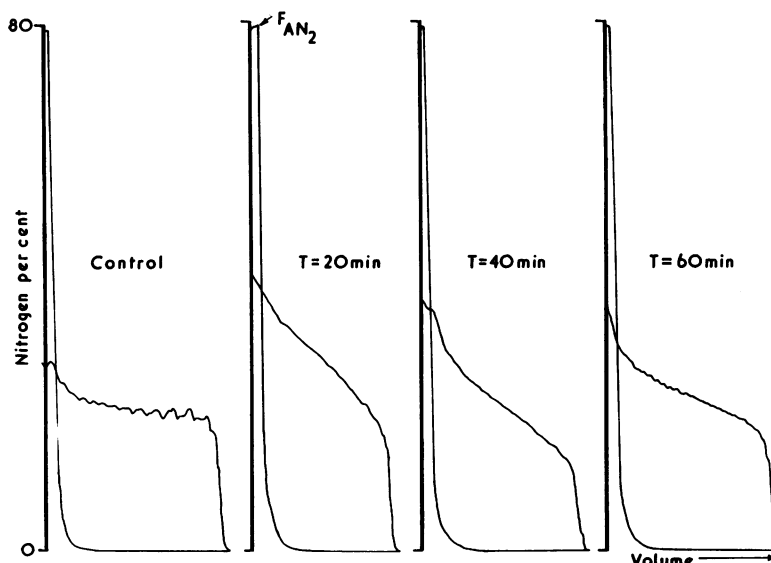


FIG. 1. Pattern of changes in one subject in the closing volume tracings before and after intramuscular administration of 15-me $PGF_{2\alpha}$. $N_2\%$ is depicted on the ordinate and inspired and expired volume on the abscissa.

where

$$RV = TLC - VC.$$

TLC was derived from the analysis of a single expiration:

$$TLC = ((VC_1 - V_{DA}) \times F_{AN_2} - V_{DS} \times \bar{F}_{AN_2}) / (F_{AN_2} - \bar{F}_{AN_2})$$

where V_{DA} = apparatus dead space = 150 ml

V_{DS} = subject dead space = 150 ml

F_{AN_2} = the endexpiratory alveolar nitrogen concentration.

\bar{F}_{AN_2} = mean alveolar nitrogen concentration = $A/(VC_e - 150)$

where A = area under the expired nitrogen concentration versus volume curve in ml \times nitrogen concentration.

Radiospirometry using ^{133}Xe was introduced by Ball *et al.* (1962).

The regional blood flow of the lung and the regional ventilation were studied according to the method described by Andersen, Johansen, and Hyldebrandt (1976) and Andersen and Rasmussen (1975). Four horizontal collimated detectors were placed in a vertical row over the back of the right lung field. The detector diameter was 4.5 cm and the distance between the apical and basal detectors was 18 cm. The top of the apical detector was placed below the line between the right clavicle and the upper edge of the right scapula, after inspiration to TLC. ^{133}Xe was injected after 20 minutes in the sitting position in doses of 0.7 mCi and flushed through a right antecubital vein with 10 ml saline during breath-holding with open glottis at TLC. The perfusion height (H)—deflection from base line during breath-holding—is proportional to the regional pulmonary blood flow. After injection of ^{133}Xe rebreathing was carried out into a closed system, consisting of a CO_2 absorber and a 4-litre rubber bag filled with oxygen. After equilibration (about 2 min), as judged by a constant relationship between the four zones, three inspirations to TLC were performed producing a mean rebreathing height (R) proportional to the number of alveoli in the respective detector fields. The regional perfusion for each of the four detectors was expressed as the perfusion index: $(PI)_n = (H_n / (H_1 + H_2 + H_3 + H_4)) / R_n (R_1 + R_2 + R_3 + R_4)$ where n = detector number = 1, 2, 3, or 4. Detector 1 refers to the apical and detector 4 to basal lung section. The units of PI are therefore: Flow (arbitrary units) per alveolus. The regional ventilation was obtained by analysing the regional washout curves during normal breathing after breath-holding at TLC.

The curves consist after subtraction of background level of washout by means of alveolar ventilation,

apart from the tail end of the curve; here there is a build-up of radioactivity in lung tissue and chest wall during the test and in addition xenon from the systemic circulation begins to recirculate.

The washout curves were therefore analysed in a manner that eliminated factors other than the pure washout from the alveoli. The washout curves were depicted in semilogarithmic plots. It is possible by means of the rate constant ($k_1 \text{ min}^{-1}$) and the intersection point ($a_1 \text{ Cps}$) to calculate the exponential function ($a_1 \cdot e^{-k_1 \cdot t}$) covering the tail part of the curve. The residual part of the curve is treated in the same way after subtraction of $a_1 \cdot e^{-k_1 \cdot t}$ from the original count rates; this gives rise to a second rate constant ($k_2 \text{ min}^{-1}$), which reflects the regional alveolar ventilation (peeling-off technique).

In order to eliminate the influence of the breathing frequency, the rate constants for each detector ($k_{2,n}$) are calculated as a per cent of the total in each trial ($V_n = \text{ventilation index} = k_{2,n} \cdot 100 / (k_{2,1} + k_{2,2} + k_{2,3} + k_{2,4})$, where n = detector number = 1, 2, 3 or 4).

Forced expiratory volume (FEV_1) was measured with a pneumotachograph (Godart) and a Fleisch tube.

The cardiac output and the transthoracic electric impedance (Z_0) were measured by the Minnesota impedance cardiograph model 304A as designed by Kubicek *et al.* (1966). Z_0 is a function of thoracic fluid volume (Luepker, Michael, and Warbasse (1973).

PROCEDURE OF THE INVESTIGATION Three acceptable closing volume tracings were obtained at control level (before the administration of 15-me PGF_{2α}); these were followed by three measurements of FEV_1 , after which regional ventilation/perfusion was studied twice, followed by one rebreathing manoeuvre. One closing volume tracing was obtained five minutes after 250 μg 15-me PGF_{2α} had been administered in the gluteal muscle. One closing volume tracing was taken followed by two measurements of FEV_1 and one study of the regional ventilation and perfusion and finally by one more closing volume tracing at 20, 40, and 60 minutes. Cardiac output was measured in four patients with the impedance method before and after the administration of 15-me PGF_{2α}, and in one patient the radial artery was punctured and samples were removed for blood gas analysis at control level and 20 minutes after the administration of 15-me PGF_{2α}.

The mean values of the above measurements after the administration of PGF_{2α} were compared with those obtained before the administration (control values) using the Wilcoxon matched-pairs signed-ranks test (Siegel, 1956).

RESULTS

Nausea and menstrual cramps occurred in all patients, but none of the patients experienced any cardiopulmonary symptoms, in particular no dyspnoea. Further, no change of the character of the normal breath sounds, as evaluated by auscultation of the chest, occurred. All the patients passed loose stools within the first two hours of the administration of 15-me PGF_{2a}.

The results of the single-breath nitrogen test and forced expiratory manoeuvres are shown in Table I. A decrease in CV% was found 20 minutes after the administration of 15-me PGF_{2a} in spite of a concomitant decrease in vital capacity ($P < 0.01$). This is in agreement with the findings of a decrease in the absolute value of phase IV in mm ($P < 0.01$), whereas CC% increased ($P < 0.05$). The changes in CV% and CC% were only slight, whereas the change in the slope of phase III showed a pronounced increase (271%) ($P < 0.01$). Residual volume and residual volume in per cent of TLC (RV/TLC%) both showed a significant increase ($P < 0.01$), whereas TLC did not change ($P > 0.05$). A decrease of 9% in FEV₁ at 20 minutes was seen ($P < 0.05$). The above measurements from the single-breath nitrogen test together with the subdivisions of lung volume and FEV₁ returned to control levels after 40 minutes except for the values of the slope of the alveolar plateau (slope III) which were still raised at 60 minutes ($P < 0.05$). The result of the qualitative analysis of the closing volume curves (Fig. 1) showed lack of cardiogenic oscillations ($P < 0.05$) and curvilinear take-off from the alveolar plateau ($P < 0.05$) at 20 minutes. The cardiac output and Z₀ showed no change after the administration of

15-me PGF_{2a} in four subjects. The arterial oxygen tension of one subject fell from 89 (control) to 73 mmHg 20 minutes after 15-me PGF_{2a}, whereas arterial carbon dioxide tension (Paco₂) (31 to 30 mmHg) and pH (7.43 to 7.43) remained unchanged.

The results of the radiosprometry (regional perfusion and ventilation) are shown in Table II. The control values of regional perfusion and ventilation showed a positive gradient from the apical to the basal lung section. A redistribution of both regional ventilation and perfusion was seen after the administration of 15-me PGF_{2a} (Figs. 2 and 3). A significant increase of perfusion in the upper part of the lung (P₁ and P₂) ($P < 0.01$) and a decrease in the lower (P₃ and P₄) was found ($P < 0.05$) after 20 minutes. After 40 and 60 minutes there was no significant change in the distribution of regional perfusion as compared to control values ($P > 0.05$). At 20 minutes a positive perfusion gradient from apical to basal lung section was still present, which is in contrast to the changes seen in the regional ventilation where the apical ventilation exceeded the basal ventilation. At 20, 40, and 60 minutes there was a significant decrease in basal ventilation (V₃ and V₄) compared to control values.

DISCUSSION

Our findings of a significant decrease in FEV₁ of 9% indicate that bronchoconstriction is induced after the administration of 15-me PGF_{2a}. This abnormality of lung function is further demonstrated by 271% increase in unevenness of distribution of alveolar ventilation (slope of the alveolar plateau), an increase in residual volume, a decrease in vital capacity, and

TABLE I
PULMONARY FUNCTION BEFORE AND AFTER 15-me PGF_{2a}

	CV %	Phase IV (mm)	CC %	Slope III (% N ₂ /l BTPS)	VC (ml BTPS)	TLC (ml BTPS)	RV (ml BTPS)	RV/TLC %	FEV ₁ (ml BTPS)
Control									
Mean	14.5	12.6	35.1	1.24	3435	4513	1071	23.6	3075
SD	7.6	6.3	6.7	0.64	390	482	226	4.2	377
N	10	10	10	10	10	10	10	10	8
5 min									
Mean	12.4	10.4	35.7	1.42	3434	4669	1236	26.6	—
SD	4.2	3.8	5.4	0.97	450	472	272	5.6	—
N	7	7	7	7	7	7	7	7	—
20 min									
Mean	11.3*	8.8**	38.5*	4.61**	3054**	4358	1306**	30.2**	2790*
SD	6.4	4.8	5.6	2.38	517	549	234	4.5	453
N	10	10	10	10	10	10	10	10	8
40 min									
Mean	12.8	10.2	36.7	4.00*	3400	4487	1228	27.3	3008
SD	5.3	3.9	5.2	2.08	533	584	278	4.9	360
N	7	7	7	7	7	7	7	7	6
60 min									
Mean	12.1	10.6	33.9	2.02*	3530	4685	1156	24.5	3093
SD	5.4	4.5	5.0	1.59	434	482	290	5.7	371
N	6	6	6	6	6	6	6	6	6

* $P < 0.05$ ** $P < 0.01$

TABLE II
REGIONAL PERFUSION (FLOW/ALVEOLUS) AND REGIONAL VENTILATION BEFORE AND AFTER 15-me PGF_{2α}

	Perfusion Index				Ventilation Index			
	P ₁	P ₂	P ₃	P ₄	V ₁	V ₂	V ₃	V ₄
Control values								
Mean	0.606	0.790	1.118	1.275	17.0	23.9	26.6	32.5
SD	0.073	0.032	0.049	0.090	4.6	1.6	1.6	3.8
20 min								
Mean	0.709**	0.895**	1.100*	1.135*	24.9	26.9	24.4**	23.9**
SD	0.149	0.114	0.082	0.216	4.6	10.2	2.9	7.7
40 min								
Mean	0.654	0.814	1.145	1.189	23.1	22.3	25.8*	28.9*
SD	0.088	0.102	0.064	0.158	2.7	2.3	1.4	3.7
60 min								
Mean	0.604	0.890	1.124	1.229	18.7	27.3	23.9*	27.7*
SD	0.091	0.088	0.072	0.162	3.3	4.2	1.1	2.6

P = index of perfusion (flow/alveolus).
V = index of ventilation in per cent of total.
Index numbers refer to detector numbers: 1 = apical and 4 = basal lung section.
* P < 0.05.
** P < 0.01.

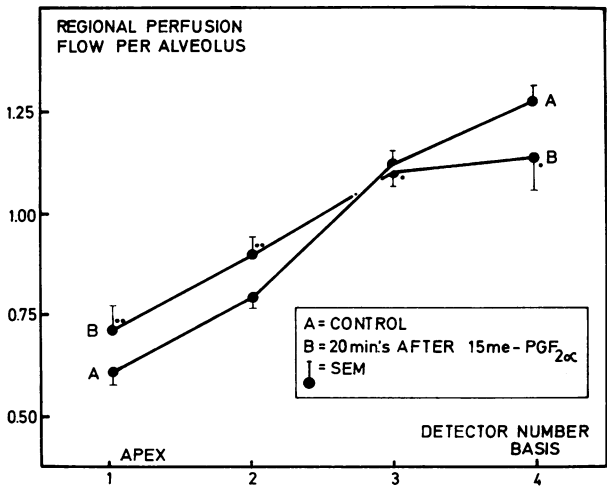


FIG. 2. Distribution of mean values of regional perfusion (flow/alveolus) in the sitting position before and after intramuscular 15-me PGF_{2α}. A denotes resting perfusion values and B denotes perfusion distribution 20 minutes after administration of intramuscular 15-me PGF_{2α}.

in one subject, a decrease in arterial oxygen tension. The slope of the alveolar plateau or the unevenness of alveolar ventilation was the most sensitive measurement in spite of the reproducibility of control values being 15%, which is greater than that of FEV₁; the latter was 1% (P < 0.01). In addition, the slope of phase III revealed the greatest changes. Finally, the slope of the alveolar plateau showed the longest duration of abnormal values.

The increase in slope of the alveolar plateau can be explained by stratified and/or regional inhomogeneity (Buist and Ross, 1973b). The marked decrease

in basal ventilation throughout the study indicates that the maldistribution of alveolar ventilation must be due mainly to a decrease of ventilation in the basal lung sections, giving rise to regional inhomogeneity.

The closing volume increased after histamine-induced bronchoconstriction, as measured by the bolus method, whereas it decreased with the nitrogen method. This was explained by the inability of the nitrogen method to establish a concentration gradient in cases of 'air trapping' (Benson, Newberg, and Jones, 1975). Our method of measuring closing volume is a modified bolus technique (Oxhøj and Bake,

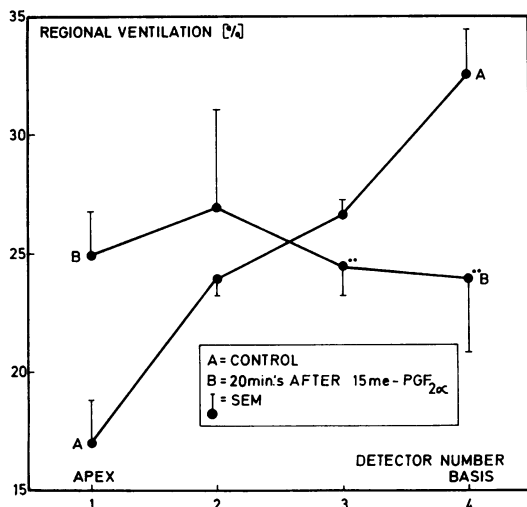


FIG. 3. Distribution of the mean values of regional ventilation before and after intramuscular 15-me PGF_{2α}. A denotes resting values and B ventilation distribution 20 minutes after administration of 15-me PGF_{2α}. Detectors 3 and 4 correspond to lung base. ** Denotes significant difference ($P < 0.01$).

1974); a dead space within the apparatus of 150 ml when added to the anatomic dead space gives a nitrogen bolus of 300 ml; thus, an increase in closing volume would be expected. However, we found a decrease in closing volume after the induction of bronchoconstriction. A concomitant increase in the slope of the alveolar plateau was found similar to that seen after acetylcholine-induced bronchoconstriction when using the single-breath oxygen test (Stanescu *et al.*, 1968). The increase in the degree of uneven ventilation could thus obscure a premature airway closure. The influence of methodological 'noise' is less pronounced when using a pure bolus method, as the rise of the alveolar plateau is smaller in persons with uneven ventilation. According to Buist and Ross (1973b), a simultaneous increase in closing volume per cent and slope of alveolar plateau is seen in the early stage of chronic airways obstruction. On the contrary, we have found a decrease in closing volume when the slope of the alveolar plateau increases. Thus, when a pathological increase in the slope of the alveolar plateau is present, low values of phase IV or closing volume could be misleading.

Several factors influence the phenomenon of airway closure, ie, changes in thoracic blood volume, peribronchial oedema, and changes in bronchial muscle tone and elastic recoil of the lungs

(Andersen *et al.*, 1974). Our findings of an unchanged Z_0 suggest that it is unlikely that interstitial oedema or a change in thoracic blood volume plays any significant role in the present study. A considerable decrease in basal ventilation as observed in this investigation could suggest early airway closure in the dependent parts of the lung in agreement with the findings of Benson *et al.* (1975) when using the bolus method. The findings of the decrease in CV% in our study could be explained by a more even distribution of the inspired oxygen to the apical and middle lung sections, obliterating the apical/basal nitrogen concentration gradient necessary for detection of early onset of airway closure.

On the other hand, the obliteration of the cardiogenic oscillations of the alveolar plateau and the curvilinear take-off has been considered an indicator of chronic airways obstruction (Benson and Mansell 1975). The changes induced after 15-me PGF_{2α} might thus be caused by an increase in smooth muscle tone in the small airways, leading to a decreased tendency to airway closure; this would explain the decrease in CV% in our study. Should this be the case the increased closing volume found by the bolus method could be an artefact.

When subdivisions of lung volume are estimated with the gas dilution method, there is a danger of underestimation due to the possible development of non or poorly ventilated areas of the lung (Buist and Ross, 1973a). In spite of this an increase in residual volume was found in all our patients. Increased residual volume without a concomitant increase in total lung capacity was found after provoked asthma using either the gas dilution method (Woolcock *et al.*, 1971) or body plethysmography (Lovejoy *et al.*, 1961; Stanescu, Frans, and Brasseur, 1973; Cade *et al.*, 1971); this agrees with our findings. The increase in residual volume could be caused by an increase in the amount of trapped gas in the lung, ie, non-communicating alveoli (Lovejoy *et al.*, 1961) and/or changes in the lung mechanics (Cade *et al.*, 1971). If non-ventilated areas give rise to the increase in residual volume in this study, they would not be reflected by the gas dilution method, where a decrease in residual lung volume would be expected. This indicates that changes in the mechanical properties of the lung, the chest wall or both are induced by 15-me PGF_{2α}, in agreement with the findings of a rapid change in the lung mechanics induced by methacholine in asthmatic subjects (Cade *et al.*, 1971) and with the findings of a decrease in elastic recoil in asthmatic patients (Gold, Kaufman, and Nadel 1967; Finucane and Colebatch, 1969).

Our findings of a redistribution of blood flow towards the apex with no change in cardiac output

could be caused by an increase in the pulmonary artery pressure, as has been shown during the infusion of PGF_{2α} (Secher and Andersen, 1976). The more pronounced redistribution of ventilation than perfusion caused mismatching of ventilation and perfusion, as demonstrated by a fall in arterial oxygen tension. Our findings point to a change in perfusion being secondary to the more marked bronchoconstriction. The more pronounced effect of 15-me PGF_{2α} on lung base could be explained by a larger amount of prostaglandin being metabolized in that part of the lung where the blood flow is greatest. Another factor may be the lower oxygen tension in the basal alveoli in the sitting position (West, 1970) as it has been demonstrated that the effect of prostaglandin is accentuated by hypoxia in the isolated cat lung (Lonigro and Dawson, 1975).

CONCLUSION

It has been shown that 15-me PGF_{2α} has induced airways obstruction, mainly confined to the dependent 'small airways'. The 15-me PGF_{2α} caused a response at the sites of larger and of 'small' airways, but the response of the larger airways was less pronounced and of shorter duration. The increased slope of the alveolar plateau and the decreased regional ventilation of the lower section, even after 60 minutes, indicated residual abnormality of the 'small airways'. It was demonstrated that CV% was of no value as an indicator of the functional abnormality induced in the airways by the 15-me PGF_{2α} as it became normal in spite of abnormalities in all the other measurements. The above-mentioned changes in the airways are consistent with an increase of smooth muscle tone in the small airways giving rise to the fall in CV%. This fall in CV% could reflect physiological reality, ie, decreased tendency towards airway closure, or could be an artefact as the curvilinear take-off from the alveolar plateau makes the measurement of the closing point difficult. Therefore, the CV% should not be used in cases of pathological increase of slope of the alveolar plateau. Our findings of an increase in closing capacity (CC%) with no change in TLC is explained by the increase in residual volume, which means that the parameter CC% gives no more information than measurement of residual volume. The detection of uneven distribution of alveolar ventilation, expressed as the slope of the alveolar plateau in the modified single breath nitrogen test, is therefore more sensitive than the conventional spirometric test.

As a significant degree of airways obstruction has been induced by 15-me PGF_{2α}, the drug should be used with caution for termination of pregnancy in women with cardiopulmonary disease.

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Requests for reprints to: Dr. L. H. Andersen, Department of Clinical Physiology, Odense University Hospital, DK-5000, Odense, Denmark.