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Pulmonary capillary blood volume in women: normal values and the effect of oral contraceptives

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Pulmonary capillary blood volume (V_c) was determined in 30 young women, 14 of whom were taking oral contraceptives. Duplicate estimates of V_c in the 16 women not taking contraceptives showed a significant increase in the second half of the menstrual cycle. Formulae for prediction of V_c in women were derived for the first and second halves of the cycle. V_c was shown to be of the same order in women taking contraceptives containing oestrogen and progestogen as in those in the premenstrual phase of the cycle. Possible causes of these findings and their relevance to the diagnosis of pulmonary thromboembolic disease are discussed.

Oral contraceptives appear to have many different actions on the vascular system. On the one hand, they may cause vasodilatation (Goodrich and Wood, 1964) and an increase in blood volume (Walters and Lim, 1969) while, on the other, they may contribute to intravascular coagulation (Dugdale and Masi, 1969; Inman, Vessey, Westerholm, and Engelund, 1970) and endarteritis (Irey, Manion, and Taylor, 1970). In the investigation of obliterative disease of the pulmonary vascular bed it has been suggested that estimation of the pulmonary capillary blood volume (V_c) may be a helpful diagnostic tool (Nadel *et al.*, 1966). The present study was planned to determine the normal values for V_c in females, and to find if oral contraceptive therapy alters these values.

METHODS

Thirty women, aged between 18 and 35 years, were studied. All were non-smokers or smoked fewer than five cigarettes per day. Fourteen of the subjects were taking oral contraceptives (oestrogen plus progestogen) at the time of study. The other 16 were studied at two separate times in the menstrual cycle—between 7 and 10 days after and again between 2 and 4 days before the onset of menstruation. In addition, nine normal men were each studied on two occasions in order to determine the relative error of the techniques. The physical characteristics of the subjects and details of contraceptive therapy are given in Tables I and II.

The techniques used were based on those of McNeill, Rankin, and Forster (1958) using the formula $1/D_L = 1/D_m + 1\theta V_c$, derived by Roughton and Forster (1957), where D_L=transfer factor of the lung for carbon monoxide, D_m=diffusing capacity of the pulmonary membrane, and θ= the reaction rate of haemoglobin with carbon monoxide *in vitro*. Duplicate determinations of D_L were made at three different alveolar oxygen tensions, using the method of Ogilvie, Forster, Blakemore, and Morton (1957) except that neon rather than helium was used in the gas mixture. For the low oxygen measurements, a gas containing 0.4% carbon monoxide, 0.4% neon, and 21% oxygen in nitrogen was used. For the high oxygen measurements 0.4% carbon monoxide and 0.4% neon in oxygen was used.

The subjects were studied in the sitting position, smokers not being tested until at least three hours after their last cigarette. Two single breath manoeuvres were carried out using the low oxygen gas. High oxygen gas was then substituted and the subjects carried out two further single breath manoeuvres. Finally, two more measurements of D_L were made using the high oxygen gas after the subjects had breathed 100% oxygen for one to two minutes. In all cases care was taken to prevent a Valsalva manoeuvre and at least five minutes were allowed to pass between each test.

Neon and carbon monoxide in the gas samples were analysed by a Beckman gas chromatograph and oxygen tension was measured with an I.L. electrode. The subjects' total lung capacities were measured in a constant volume body plethysmograph (DuBois *et al.*, 1956) and residual volume was obtained by subtraction of vital capacity after both volumes had been corrected to S.T.P.D.

CALCULATIONS Transfer factor was calculated from the formula of Ogilvie *et al.* (1957). The reaction rate of carbon monoxide with haemoglobin, θ, was obtained from the formula $1/\theta = 0{\cdot}33 + 0{\cdot}0057\ P_{cO_2}$,

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where P_cO_2 is the oxygen tension in the pulmonary capillary. The derivation of θ is based on the work of Roughton and Forster (1957) assuming a value for λ (the ratio of permeability to carbon monoxide of the membrane of the red cell to its interior) of 2·5. The pulmonary capillary oxygen tension was estimated from the expired alveolar oxygen tension (P_cO_2) from the formula $P_cO_2=(P_cO_2+5)-\frac{300}{D_L\times 1{\cdot}23}$ (McNeill *et al.*, 1958).

A formula for regression of $1/D_L$ on $1/\theta$ was calculated using the method of least squares. The slope of this line represents $1/V_c$ and the intercept gives the reciprocal of the diffusing capacity of the pulmonary membrane, D_m.

STATISTICAL METHODS In order to compare the results in the controls with those in the subjects taking contraceptive tablets, values for D_L, V_c and D_m were divided by the subject's total lung capacity. The groups were then tested by the *t* test for independent samples, the significant values for *t* at the 5% level for these data being equal to or greater than 2·048.

To compare the results obtained in the control group at the two different stages of the cycle, the *t* test for paired samples was used. For these data the significant value of *t* at the 5% level was equal to or greater than 2·131.

Correlation coefficients (r) between D_L, V_c and D_m and height, surface area and total lung capacity at S.T.P.D. were calculated in the controls at both stages of the cycle. The values of r showing linearity but not a one to one relationship fall between 0·5 and 0·97. The relative error of duplicate measurements in the male controls was calculated using an analysis of the components of variation.

TABLE I

CONTROL SUBJECTS

Subject No.	Age (yr)	Height (in)	Weight (lb) (a)	(b)	Total Lung Capacity at STPD (ml)	(D_L) Lung Transfer Factor (ml/min/mmHg) (a)	(b)	(V_c) Pulmonary Capillary Blood Volume (ml) (a)	(b)	(D_m) Membrane Diffusing Capacity (ml/min/mmHg) (a)	(b)
1	18	62·5	108	108	2870	20·5	21·3	60·6	69·4	30·7	30·0
2	23	64	111	111	2940	25·7	25·8	57·4	84·7	45·3	36·2
3	20	63	120	127	3110	26·4	22·9	68·8	75·6	42·4	32·7
4	29	63	123	123	3350	22·4	23·5	57·3	63·2	37·9	37·7
5	23	67	136	137	3420	25·4	30·5	81·5	95·7	36·6	44·7
6	21	60·5	101	101	3440	35·4	34·7	73·4	94·7	68·4	56·2
7	22	67	170	172	3560	30·9	33·3	92·7	96·6	46·2	50·9
8	28	62	132	132	3580	26·9	29·7	74·0	72·6	50·0	50·2
9	18	65	135	135	3590	25·4	25·9	69·3	76·0	39·8	39·5
10	21	62	114	111	3620	26·6	30·7	70·3	80·3	53·0	49·6
11	25	69	143	143	3800	23·2	28·8	74·6	106·3	33·4	38·9
12	31	70	143	141	4420	29·1	28·7	86·7	96·4	44·2	40·3
13	28	69	168	170	5050	44·4	43·5	138·9	151·7	65·6	60·5
14	20	69	150	150	5300	41·2	38·4	87·3	106·3	78·7	61·2
15	19	70	166	166	5330	41·40	42·4	119·0	132·1	63·2	64·1
16	20	69	128	128	5420	39·9	46·6	121·7	129·5	58·6	72·1
Mean	22·9	65·8	134·3	134·7	3925	30·3	31·7	81·5	95·7	49·6	47·8
S.D.	4·1	3·3	21·5	21·9	881	7·7	7·7	26·3	24·9	13·8	12·3

a = first half of menstrual cycle; b = second half of menstrual cycle

TABLE II

SUBJECTS ON ORAL CONTRACEPTIVES

Subject No.	Age (yr)	Height (in)	Weight (lb)	Type of Contraceptive Therapy	Time on Oral Contraceptives (yr)	Total Lung Capacity at STPD (ml)	D_L (ml/min/mmHg)	V_c (ml)	D_m (ml/min/mmHg)
17	21	61	103	Ovulen-21	1	2790	23·4	68·0	34·5
18	25	60	152	Ovulen-21	3	3110	22·4	78·5	31·1
19	26	63	118	Enovid-E	5	3390	33·9	117·7	47·0
20	22	63	116	Ovral	0·6	3440	31·3	84·8	52·1
21	19	63	120	Norinyl	1	3520	25·5	95·2	34·4
22	24	64·5	149	Ortho-Novum	3	3520	27·7	71·0	45·3
23	20	60·5	101	Ovral	0·5	3570	33·2	81·8	55·9
24	24	65	153	Ortho-Novum	4	3600	26·2	83·9	37·7
25	22	66	135	Ovulen-21	2	3690	28·1	97·0	39·5
26	27	63·5	123	Ovral	0·6	3730	37·0	102·4	58·1
27	27	64	123	Ortho-Novum	4	3740	31·7	93·5	48·6
28	25	66	113	Ortho-Novum	2·5	3790	31·8	104·3	45·6
29	25	67	163	Norlestrin	2·5	4030	29·4	88·4	43·8
30	23	66·5	127	Ovulen-21	0·6	4380	36·9	103·5	57·6
Mean	23·6	63·8	128		2·2	3590	29·9	90·7	45·1
S.D.	2·6	2·2	19		1·5	377	4·6	13·9	8·85

RESULTS

The results in the control women in the two stages of the menstrual cycle are recorded in Table I and in the women taking oral contraceptives in Table II. When the values for D_L, V_c, and D_m in the two stages of the cycle are compared, there is found to be a significant increase in V_c in the second half of the cycle (t=5·07, critical value for t=2.131) while D_L and D_m do not vary significantly (t=1·63 and −1·08 respectively). Comparing the subjects on contraceptive therapy with the controls, the only significant difference found was in V_c corrected for total lung capacity between the controls during the first half of the cycle and the subjects on contraceptives (Tables III and IV).

TABLE III

MEAN RESULTS IN CONTROLS AND SUBJECTS ON ORAL CONTRACEPTIVES

	No. of Subjects	D_L Total Lung Capacity (ml/min/mm Hg/l)		V_c Total Lung Capacity (ml/l)		D_m Total Lung Capacity (ml/min/mm Hg/l)	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
First half of cycle	16	7·79	1·05	21·15	2·92	12·73	2·70
Second half of cycle	16	8·09	0·96	24·44	3·49	12·20	1·85
Subjects on pill	14	8·32	0·97	25·30	3·44	12·53	2·02

TABLE IV

t VALUES—COMPARISON OF CONTROLS WITH SUBJECTS TAKING ORAL CONTRACEPTIVES

	Controls (1st half cycle) *v* Subjects on Oral Contraceptives *t*	Controls *v* (2nd half cycle) *t*
Transfer factor	−1·50	−0·65
Pulmonary capillary blood volume	−3·58	−0·67
Membrane diffusing capacity	0·23	−0·47

Critical value for $t = \pm 2{\cdot}048$ at 5% level of significance.

From the duplicate measurements in the male controls, the relative error of repeated determinations was found to be 5·6% for D_L, 7·3% for V_c, and 11% for D_m (Table V). The results were also found to be repeatable for three women in whom duplicate measurements were made at the same phase of the menstrual cycle (Table VI).

The relationships between D_L, V_c, D_m and height, surface area and total lung capacity were tested in the controls at both stages of the cycle. The values of r are given in Table VII. The best predictor of D_L, V_c, and D_m at either stage is total lung capacity (at S.T.P.D.). Prediction formulæ

TABLE V

DUPLICATE DETERMINATIONS IN MALES

Subject	D_L (ml/min/mmHg)		V_c (ml)		D_m (ml/min/mmHg)	
	1	2	1	2	1	2
a	31·2	34·2	101·3	105·8	45·1	52·4
b	31·6	34·5	79·5	97·7	52·8	53·1
c	32·5	39 3	122·3	114·4	44·3	59·9
d	35·4	37·6	104·0	91·5	53·7	67·1
e	40·1	39·6	175·0	165·3	48 3	52 4
f	39·3	41·2	123·5	104·0	57·8	68·9
g	43·3	43·5	122·3	140·2	68·2	63·5
h	42·3	45·1	111·5	121·0	69·4	60·5
i	48·7	51·9	163·1	164·8	69·9	76·7
Relative error	5·6%		7·3%		11%	

TABLE VI

DUPLICATE DETERMINATIONS IN WOMEN AT SAME STAGE OF MENSTRUAL CYCLE

Subject		D_L (ml/min/mmHg)	V_c (ml)	D_m (ml/min/mmHg)
F.R.	1	30·7	80·3	49·6
	2	31·1	87·5	48·9
J.S.	1	29·9	74·0	50·0
	2	26·9	72·6	50·2
M.P.	1	25·7	70·9	40·0
	2	24·9	72·8	37·5

TABLE VII

CORRELATION COEFFICIENTS IN CONTROL SUBJECTS

	Transfer Factor		Pulmonary Capillary Blood Volume		Membrane Diffusing Capacity	
	(a)	(b)	(a)	(b)	(a)	(b)
Total lung capacity	0·86	0·88	0·85	0·83	0·70	0·83
Height	0·50	0·58	0·70	0·75	0·22	0·43
Surface area	0·54	0·56	0·74	0·71	0·26	0·44

a = first half of menstrual cycle.
b = second half of menstrual cycle.

for these measurements based on total lung capacity at S.T.P.D. (TLC) are given below:

(*a*) First half of the cycle
$D_L = 7{\cdot}42\ TLC + 1{\cdot}37$ (r=0·86)
$V_c = 23{\cdot}17\ TLC - 7{\cdot}6$ (r=0·85)
$D_m = 10{\cdot}98\ TLC + 6{\cdot}54$ (r=0·70)

(*b*) Premenstrually
$D_L = 7{\cdot}64\ TLC + 1{\cdot}70$ (r=0·88)
$V_c = 23{\cdot}4\ TLC + 3{\cdot}84$ (r=0·83)
$D_m = 11{\cdot}61\ TLC + 2{\cdot}21$ (r=0·83).

DISCUSSION

Estimation of pulmonary capillary blood volume has been suggested as a method for investigation

of occlusive disease of the small pulmonary arteries and may be of particular value in subjects with multiple small emboli leading to pulmonary hypertension (Nadel *et al.*, 1966). However, the value of such a test must depend on a knowledge of the results obtained in normal subjects.

Although a number of authors have recorded normal values for V_c and D_m in their laboratories (McNeill *et al.*, 1958; Lewis, Lin, Noe, Komisaruk, 1958; Ross, Maddock, and Ley, 1961; Daly, Ross, and Behnke, 1963; McCredie, Lovejoy, and Yu, 1964; and Krumholz, 1966), there has been little agreement on the normal range. In particular, values for D_m have varied very widely in different series and even in different patients in the same series. However, most authors find the techniques show good repeatability in the same individual. Bucci, Cook, and Barrie (1961) produced prediction formulæ for V_c and D_m based on total lung capacity, height and surface area, finding no essential difference between male and female subjects.

The results reported in the present paper show reasonable repeatability in the male subjects and in the three female subjects in whom the test was repeated at the same time in the cycle. The values recorded for D_L and V_c are somewhat higher than in other series. This may be related to the use of the body plethysmograph for measuring residual volume, as this does give higher values than helium or neon methods (Reichel, 1969), although Daly *et al.* (1963) used a similar technique without getting such high values.

An increase in plasma volume in the luteal phase of the menstrual cycle has been suspected on the basis of the fall in haematocrit and gain in weight that may be found at this time (Danforth, Boyer, and Graff, 1946). At the same time in the cycle, venous tone is decreased (McCausland, Holmes, and Trotter, 1963), this effect also occurring during pregnancy and in subjects on oestrogen-progestogen contraceptives (Goodrich and Wood, 1964). Recently, it has been demonstrated that subjects show an increase in weight, plasma volume, and cardiac output when they start taking these contraceptives (Walters and Lim, 1969). Vascular changes during the menstrual cycle have been demonstrated directly in the conjunctival vessels, using slit-lamp microscopy (Landesman, Douglas, Dreishpoon, and Holze, 1953). At this site vascular dilatation occurs in the luteal phase of the cycle, followed by increased vasomotion and then vascular spasm immediately premenstrually.

Logan (1967) noticed that pulmonary capillary blood volume in five normal females was greater in the second than in the first half of the cycle, though the difference was not statistically significant. The present study shows that there is a significant variation in V_c, though not in D_L or D_m, through the menstrual cycle. In all subjects studied save one, an increase in V_c occurred the week before menstruation and this suggests that either progesterone or its combination with oestrogen is responsible. Confirmation of this comes from the finding that V_c in subjects on oestrogen-progestogen tablets is also raised compared to controls studied in the first half of the cycle.

The increase in V_c is not likely to be related to an increase in plasma volume, as determination of V_c depends on the amount of haemoglobin rather than plasma in the pulmonary capillaries. In general, there is a slight drop in haematocrit premenstrually (Danforth *et al.*, 1946) which, if it affected the estimation of V_c at all, would cause an artefactually low result. A more likely explanation of the changes observed is that progesterone, either alone or with oestrogen, causes distension of the pulmonary capillary bed, possibly secondary to an action on the arterioles or venules similar to that observed at other sites (Landesman *et al.*, 1953; McCausland *et al.*, 1963; and Goodrich and Wood, 1964). It is not easy to understand why these hormones should have a dual action on respiration, acting both as a respiratory stimulant (Goodland, Reynolds, McCoord, and Pommerenke, 1953; Döring, Loeschcke, and Ochwadt, 1950) and as a pulmonary vasodilator. Whether this second effect may contribute to the hypocapnia of pregnancy and of the luteal phase by reducing the physiological dead space is a matter for speculation.

From a practical point of view, if a state of pulmonary vasodilatation exists in subjects on oral contraceptives, arteriovenous shunts may become opened and cause zones of apparent underperfusion on lung scans which might be attributed to vascular occlusion. In such circumstances determination of V_c should be helpful. If V_c is found to be higher than the predicted normal for females in the first half of the cycle, significant occlusion of the pulmonary vascular bed is unlikely to be present. On the other hand, a value for V_c lower than this predicted normal should arouse a strong suspicion of multiple pulmonary emboli.

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