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Continuous Registration of the CO_2 Contents in Expired Air (Capnography) in the Inhalative Provocation of Children

I. Acetylcholine Provocation of Asthmatic School-age Children*

By

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Capnography, i.e. a continuous analysis of the CO_2 contents of expired air, is recommended for the examination of asthmatic children by means of inhalative provocation. A mathematical method for the evaluation of capnograms has been elaborated. The method is compared with volumetric and integrated spirometry. Fifty-five children suffering from bronchial asthma have been examined and the results were compared with those obtained in 14 hospitalized symptom-free children with normal respiratory organs. Comparison between spirography and capnography revealed the following advantages of the latter method.

(i) Capnography approaches pathologic phenomena from the angle of gas exchange.

(ii) The method admits of collecting data during quiet breathing and eliminates artefacts.

(iii) Capnography requires a minimal collaboration from the patient, one to which he can be accustomed.

(iv) The method is highly sensitive; by reducing the number of false negative reactions provocation tests become more reliable.

(v) Capnography is a routine clinical procedure suitable also for clinico-pharmacological investigations.

(vi) Decrease of the initial ratio $T_2 : T_1$ by more than 40% is regarded as the criterion of a positive reaction.

Early detection of chronic respiratory disorders is a primary task in paediatrics. Progress of therapeutical methods has made bronchial asthma a particularly significant disease, and inhalative provocation is the most realiable method for its correct diagnosis. Specific provocation with allergens facilitates aetiological diagnosis, while nonspecific (mediator) provocation is a differential diagnostic procedure [23, 24, 26, 27, 34, 53]. If the reaction is positive, inspiration of these substances in a pulverized form elicits respiratory phenomena that may be regarded as representing the model of asthmatic attacks [7, 17, 43].

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The classical and still most frequent method for the registration of induced asthmatic attacks is spirometry. Data regarding the rate of air flow are more valuable in obstructive airway diseases of asthmatic nature. Respiratory changes can be followed by the behaviour of pulmonary flow resistance as registered by means of oesophageal manometry [43]. The nitrogen washout (clearance) method has been employed for determining air distribution [7]. The method of body plethysmography for the isolated measurement of airway resistance is steadily gaining ground. Recently, the examination of gas exchange, occurring during a paroxysm, has come into the foreground [37]. The various methods used for the examination of respiratory changes occurring during asthmatic attacks are surveyed in PETIT's monograph [41]. COLLDAHL et al. [6, 7] emphasize the importance of tests which interfere with the patients' spontaneous respiration to the least possible extent.

Most of the aforesaid methods have been adapted to paediatric conditions. The detailed and fundamental data of KRAEPELIEN, ENGSTRÖM, KARLBERG, GEUBELLE and SENTERRE collected during both spontaneous and induced attacks, are prominent among the numerous reports published on this subject [13 to 17, 19, 20, 21, 30, 31, 44, 45]. ENGSTRÖM et al. [13] were the first to apply mechanical methods of breathing in provocation tests in children. They were followed by GEUBELLE and SENTERRE [19] as also by other workers [1]. Especial interest attaches to the works of KURES [32] and VEYMOLOVÁ [51]. Several authors [25, 52] collected valuable data by the nitrogen clearance method during acetylcholine provocation. Others [19, 41] provided information gained on a large juvenile material by means of the airway interruption method. The same authors and also ENGSTRÖM et al. [13 to 17] have thoroughly tested the method of measuring airway resistance by means of body pletysmography. The disturbances of gas exchange have also been discussed [47].

All this shows that many attempts have been made at adopting sensitive methods of examination in paediatrics. The efforts are, however, limited by the lack of the children's collaboration. The aim of the present study was to elaborate a method of adequate sensitivity that would reproducibly register changes in quietly breathing children without their active collaboration.

It was thought that capnography will be suitable for a quantitative estimation of the response to acetylcholine provocation; the results were compared to those yielded by spirometry.

METHODS

Spirometry. In some of the experiments VARGHA's spirometer was used [50] which allowed to determine the vital capacity (VC) as well as the vital capacity per 1 sec (FEV_1) from which the relative TIFFENEAU number could be computed. These values were determined by means of a Godart

GM 0577 type pneumotachograph in another series of experiments, and the integrated volume served for the computation of Tiffeneau's number. A two-channel Godart type recorder was used for registration, at a paper speed of 25 mm/sec. DEMUTH's data [10] were accepted for normal and were used for reference.

Capnography. Godart's URAS-type capnograph was employed for the continuous recording of CO_2 in exhaled air. Bypass-flow sampling was done at an aspiration rate of 0.5 l/min through a soft rubber tube inserted to a depth of 3 to 4 cm in the mucus-free nasal cavity. All tubes used in the experiments measured 30 cm in length and 2 mm in diameter. A few minutes were left for the patient to accustom himself to the tube and for the restoration of quiet breathing, then the capnogram was recorded at a paper speed of 750 mm/min, by a one-channel instrument (Omniascriptor, Godart). If the result showed variable breathing, the values of several expirations were averaged. Calibration of the instrument was done by an air mixture of known CO_2 contents.

*Evaluation of the capnogram.** As the method was based on the analysis of capnograms, we had to find means to express qualitative changes of the curve in a numerical form. Practical evaluation, as employed in the present study, will only be described in this paper; details regarding mathematical, geometrical and computer analysis will be dealt with later.

All capnograms show an exponential segment which passes into and terminates with a linear province (plateau). The first indicates the interproportion between the air of the dead space and the alveolar air, the second reveals the concentration of CO_2 in alveolar air. The constant rise of the plateau is caused by the continuous influx of CO_2 arriving with the circulating blood.

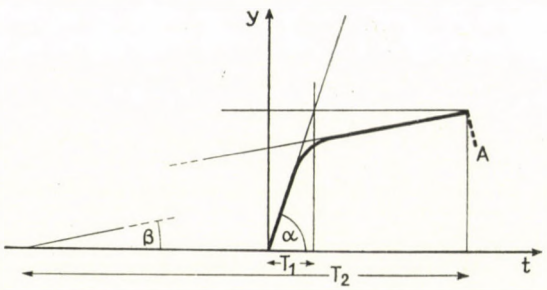

FIG. 1. Simplified method of capnogram evaluation

The physical process can be expressed by the following formula:

$$y = A\left(1 + \frac{t}{T_2} - e^{\frac{-t}{T_1}}\right)$$

where $\frac{t}{T_2}$ means the alveolar (linear) plateau and $e^{\frac{-t}{T_1}}$ the exponential part of the capnogram.

T_1, T_2 and A, the constants of the function, characterize gas exchange, and the

* VC = vital capacity; FEV_1 = vital capacity per second; $FEV_1 \frac{100}{VC}$ = relative Tiffeneau number; MBC = maximum breathing capacity; FRC = functional residual capacity; V_D = dead space volume; V_T = tidal volume.

object to be achieved is the determination of these constants from the capnogram.

Fig. 1 shows the simplified diagrammatic approximation of the accurate mathematical solution.

If $T_2 \gg T_1$ and if $t = 3\,T_1$, then $y \simeq A$

Provided the above postulates were satisfied, the practical evaluation was carried out as follows. We constructed tangents to both the exponential portion and the linear segment (plateau) which formed, each, an angle with the axis t. After marking the height A on axis y, we constructed the projections of the legs of the angles on the axis t (Fig. 1).

$\operatorname{tg}\alpha = \frac{A}{T_1}$ and $\operatorname{tg}\beta = \frac{A}{T_2}$, hence $\frac{\operatorname{tg}\alpha}{\operatorname{tg}\beta} = \frac{T_2}{T_1}$, irrespective of the value of A.

As seen, the capnograms were characterized by the quotient of the two values resulting from the said projections. The value of T_2 was mostly computed by extrapolation. Graphic illustration of the results was (in accordance with the nature of the evaluation) effected on a logarithmic scale.

Provocation. The patient was sitting during the provocation and the measurements. We determined first the initial value. Spirometry was started only after the capnogram had been registered, so as to prevent its distortion by forced breathing and hyperventilation.

After a few minutes of rest, a 0.5% solution of acetylcholine was nebulized by means of a constant-performance compressor through a spray apparatus of the Glück or Hutás—Nyiredi type. The nebulized mediator was conducted through a thick rubber tube to the mask fitted snugly to the patient's face who inhaled with the mouth open. Each inhalation lasted 30 sec during which the capnogram was recorded; in cases of changes (and sometimes even without observed changes) a spirogram was made after 3 or 4 inhalations. Provocation was continued until marked respiratory changes had appeared and in negative cases until the ninth or tenth inhalation. The quantity of acetylcholine varied from 800 to 1200 μg per 30 sec according to the type of spray apparatus. Evaluation was based on this value although, owing to discontinuous breathing, only part of it was effective pharmacologically.

Intervals between the inhalations were as short as possible, and patency of the nasal ducts was carefully observed, together with the physical signs and the general condition of the patient.

Material

The material consisted of 55 patients with bronchial asthma who were systematically treated and controlled. Table I shows the relevant data and the initial values for the patients. The patients had no attacks and received no cortisone at the time of the examination.

Fourteen symptom-free hospitalized patients with intact respiratory organs, subjected to provocation under the same experimental conditions, served as controls. Their results are listed in Table II.

Results

Data registered during the provocation of asthmatic children are shown in Table III. Average values obtained in respect of the asthmatic and the control groups are diagrammatically illustrated in Fig. 2.

Apart from certain fluctuations, in the controls the value for T_2/T_1 was not essentially affected by the provocation. Their spirometric data, too, remained within physiological limits.

On the other hand, asthmatic patients reacted markedly to the inhalation of acetylcholine. Although

the average initial values did not essentially differ from those measured in the control group, the values for T_2/T_1 dropped steeply after the first 30 sec period of inhalation. The decrease subsequently became less pronounced, since provocation was a negative case of provocation, respectively.

The reason why spirometry was performed simultaneously with capnography was to compare our method with a standard procedure in order to ascertain possible deviations and

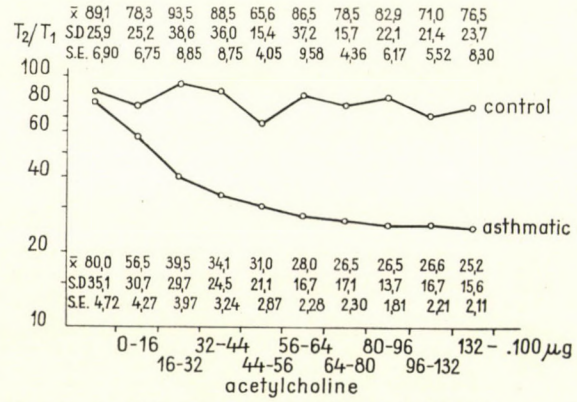

FIG. 2. Changes in average $T_2 : T_1$ ratio during acetylcholine provocation of asthmatic and healthy children

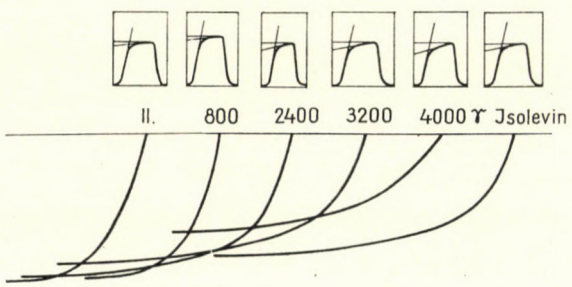

FIG. 3. Curves of illustrative cases from asthmatic group. Positive provocation test. Above: capnograms; below: spirograms

discontinued in some patients after reaching certain bottom values; when computing averages we used these terminal values, although continued provocation would undoubtedly have resulted in still lower values.

Figs 3 and 4 present the capnogram and spirogram of a positive and to determine the sensitivity of the suggested procedure. The units of measurement being different, we compared deviations with reference to the initial value and expressed them in its per cent. Results are presented in Fig. 5. With this evaluation, it was after the fourth inhalation that Tif-

TABLE I

Data and initial values for

No.	Date of test	Initials	Sex	Age, year	Length, cm	Weight, kg	Duration of disease, years	Gravity
1.	1965 VI. 16.	B. I.	♀	14	153	36	6	IV
2.	1965 XII. 8.	Sz. I.	♂	8	116	19	4	III
3.	1965 XII. 8.	V. M.	♀	8	136	20	3	I
4.	1965 XII. 17.	T. J.	♂	12	154	32	11	III
5.	1965 XII. 21.	T. M.	♀	10	142	27	2	III
6.	1966 I. 11.	T. A.	♂	14	142	35	10	III
7.	1966 I. 19	F. M.	♀	9	127	27	10	IV
8.	1966 II. 10.	S. Gy.	♂	10	149	27	9	IV
9.	1966 II. 10.	P. S.	♂	8	126	23	6	III
10.	1966 II. 24.	K. Zs.	♀	8	124	24	2	III
11.	1966 III. 7.	K. P.	♂	13	154	35	12	II
12.	1966 III. 11.	J. M.	♀	9	129	28	6	II
13.	1966 III. 16.	S. R.	♀	9	128	23	6	IV
14.	1966 III. 16.	Gy. E.	♀	13	155	42	12	II
15.	1966 III. 16.	F. M.	♀	10	132	28	8	IV
16.	1966 III. 23.	P. J.	♂	13	146	39	4	III
17.	1966 IV. 1.	V. M.	♀	11	156	45	9	I
18.	1966 IV. 3.	Sz. S.	♂	7	126	25	5	I
19.	1966 IV. 3.	K. L.	♂	6	126	25	6	II
20.	1966 IV. 6.	G. H. J.	♂	11	146	34	7	IV
21.	1966 IV. 6.	K. A.	♂	8	135	24	7	II
22.	1966 IV. 18.	Sz. I.	♂	10	139	26	6	III
23.	1966 IV. 18.	M. J.	♂	10	138	28	5	I
24.	1966 IV. 18.	H. J.	♂	11	132	28	2	III
25.	1966 IV. 27.	D. K.	♀	6	117	22	5	II
26.	1966 IV. 27.	Sz. I.	♂	14	160	40	5	II
27.	1966 IV. 27.	H. S.	♂	8	128	22	3	I
28.	1966 IV. 29.	P. P.	♂	8	124	25	8	IV
29.	1966 IV. 29.	H. A.	♂	7	123	22	6	II
30.	1966 V. 6.	T. I.	♀	8	120	21	7	III
31.	1966 V. 25.	V. G.	♂	10	136	32	7	IV
32.	1966 VII. 10.	H. J.	♂	10	133	25	8	IV
33.	1966 VII. 13.	Sz. L.	♂	11	139	30	11	II

the asthmatic children

Emphysema	Chest deformity	Normal average 1	VC measured 1	In per cents of normal	FEV_1 1	$\frac{FEV_1 \cdot 100}{VC}$ %	Capnogram T_2/T_1 estimated	Capnogram T_2/T_1 in per cents of normal
+	+	2.70	2.41	94	2.22	92	148	178
—	+	1.30	1.31	100	1.19	91	150	180
—	—	1.90	1.02	53	1.02	100	111	134
+	+	3.00	2.40	80	2.12	88	81	97
+	—	2.20	1.89	94	1.85	98	109	132
—	—	2.60	2.04	77	2.04	100	40	48
—	—	1.60	1.59	100	1.31	82	86	103
+	+	2.80	1.29	46	1.13	88	31	37
+	+	1.80	1.92	106	1.75	91	52	63
+ (atelectasis)	—	1.50	1.21	80	1.13	93	94	113
+	—	3.00	2.90	98	2.62	90	100	120
—	—	1.60	1.40	87	1.40	100	47	57
+	+	1.60	1.22	76	0.82	67	51	62
—	—	2.80	2.52	89	2.42	97	93	110
+	+	1.95	1.95	100	1.41	72	71	86
—	—	2.60	3.02	115	2.93	97	80	96
—	—	2.80	2.60	93	2.39	92	65	78
—	—	1.70	1.88	110	1.73	92	62	75
—	—	1.70	1.22	73	1.16	95	76	91
+	+	2.60	2.42	93	1.94	80	35	42
—	—	2.10	1.62	77	1.51	93	50	60
+	+	2.20	2.02	92	1.90	94	83	100
—	—	2.22	2.22	100	2.04	92	139	178
—	+	1.95	1.93	99	1.74	90	46	56
—	—	1.30	1.35	104	1.24	92	57	69
±	—	3.30	2.98	91	2.90	97	77	93
+	—	1.80	1.82	101	1.82	100	63	76
—	—	1.60	1.50	94	1.38	92	75	90
+	—	1.60	1.41	93	1.40	100	81	98
—	—	1.30	1.18	92	1.17	100	46	55
—	—	2.10	1.95	93	1.60	82	31	37
+	+	2.00	2.28	118	1.62	71	36	43
—	—	2.25	2.76	122	1.91	69	48	58

TABLE I

No.	Date of test	Initials	Sex	Age, year	Length, cm	Weight, kg	Duration of disease, years	Gravity
34.	1966 VII. 22.	K. I.	♂	11	133	26	10	I
35.	1966 VII. 22.	F. L.	♂	10	156	65	3	II
36.	1966 VII. 27.	Zs. J.	♂	7	127	20	2	III
37.	1966 VIII. 5.	Sz. Zs.	♀	8	124	25	7	III
38.	1966 VIII. 10.	B. L.	♂	9	139	32	1	IV
39.	1966 IX. 16.	L. E.	♀	8	137	37	7	IV
40.	1966 IX. 20.	Sz. K.	♂	10	139	35	4	II
41.	1966 XI. 1.	B. Sz.	♂	12	133	26	2	IV
42.	1967 III. 12.	T. M.	♀	13	154	38	2	III
43.	1967 VIII. 15.	O. E.	♀	12	137	31	11	I
44.	1967 VIII. 24.	V. S.	♂	10	126	23	9	IV
45.	1967 VIII. 29.	T. I.	♀	14	154	53	1	II
46.	1967 X. 24.	B. F.	♂	13	156	42	4	III
47.	1967 XII. 22	K. Á.	♀	8	123	21	6	I
48.	1967 XII. 22.	M. Gy.	♂	12	147	36	12	III
49.	1968 II. 2.	V. É.	♀	9	140	31	4	II
50.	1968 II. 2.	K. M.	♀	9	125	28	4	II
51.	1968 III. 1.	A. A.	♂	12	147	22	12	III
52.	1968 III. 1.	Ny. T.	♂	13	158	60	11	III
53.	1968 III. 1.	J. M.	♂	11	142	33	2	II
54.	1968 III. 19.	Á. I.	♀	10	137	25	6	II
55.	1968 VII. 12.	K. E.	♀	9	128	22	4	III

Total: 33 boys Mean age: 10.0 years
22 girls

VC and FEV_1 = in BTPS 1—31: spirometrically determined volumes
32—55: tachographically integrated volumes

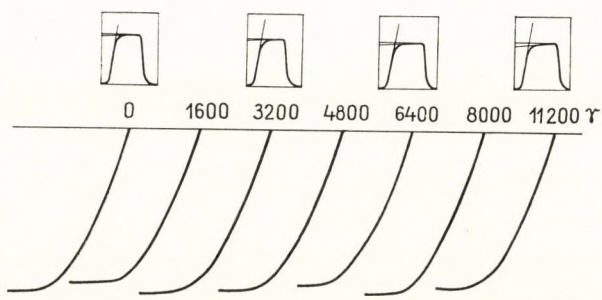

FIG. 4. Curves of illustrative cases from the control group. Negative provocation test
Above: capnograms; below: spirograms

cont.

Emphysema	Chest deformity	Normal average 1	VC measured 1	In per cents of normal	FEV_1 1	$\frac{FEV_1 \cdot 100}{VC}$ %	Capnogram T_2/T_1 estimated	Capnogram T_2/T_1 in per cents of normal
—	—	2.00	2.18	109	1.86	85	114	151
—	—	3.20	3.30	103	2.51	76	47	57
—	—	1.80	1.98	110	1.55	78	80	96
—	—	1.65	1.35	82	0.99	74	163	196
—	—	2.30	2.45	107	1.38	56	40	48
—	—	1.95	1.98	97	1.43	72	49	60
—	—	2.30	2.54	111	2.28	90	90	108
+	+	2.00	2.32	115	1.86	80	93	112
—	—	2.75	3.20	116	2.56	80	52	63
bronchiectasia	—	2.00	1.80	90	1.49	83	92	111
+	+	1.75	1.80	103	1.19	66	39	47
—	—	2.75	2.94	107	2.47	84	186	224
—	+	3.15	3.36	107	2.22	66	103	124
—	—	1.45	1.44	100	1.42	99	44	53
±	—	2.65	3.06	115	2.03	66	65	78
—	—	2.10	2.10	100	1.86	89	95	114
—	—	1.55	2.10	135	1.81	86	94	113
+	+	2.70	3.12	115	2.40	77	88	106
—	—	3.30	3.90	118	3.31	85	162	195
—	—	2.40	2.82	117	2.37	84	75	90
—	—	1.95	1.92	98	1.51	78	57	69
+	+	1.65	2.58	156	1.63	63	162	195

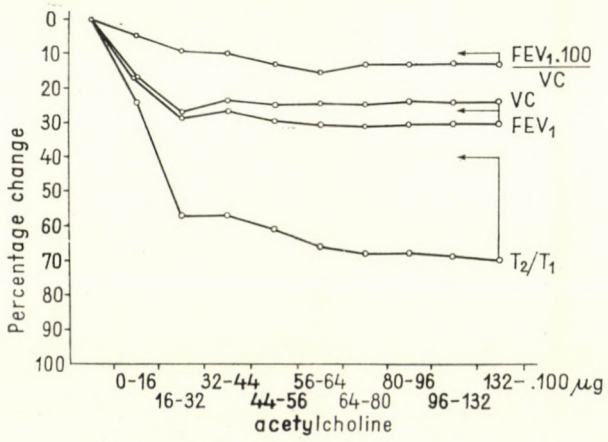

FIG. 5. Percentual changes in initial Tiffeneau number, vital capacity, vital capacity per second, and $T_2 : T_1$ ratio, in the course of acetylcholine provocation. Arrows point to alterations regarded as pathologic

TABLE II

Spirographic, capnographic and clinical data of normal

No.	Date of test	Initials	Sex	Age, years	Length, cm	Weight, kg	Diagnosis	Normal average	VC 1 measured	BTPS in per cents of normal	FEV_1 1 BTPS
1.	1965 XII. 8.	Sz. Zs.	♀	11	143	35	Tonsillitis	2.20	2.03	98	1.82
2.	1965 XII. 12	T. M.	♀	12	145	38	Poisoning	2.30	2.29	100	2.29
3.	1966 IV. 6.	G. J.	♂	7	120	24	Tonsillitis	1.50	1.45	97	1.40
4.	1966 IV. 6.	R. I.	♀	13	158	47	Enuresis	2.90	2.78	97	2.78
5.	1966 IV. 6.	N. I.	♀	10	134	29	Tonsillitis	1.80	1.85	103	1.56
6.	1966 V. 7.	B. M.	♀	13	155	41	Hyperthyroidism	2.80	2.78	100	2.55
7.	1966 V. 11.	K. I.	♂	12	144	37	Perinephritic abscess	2.50	2.40	98	2.38
8.	1966 V. 11.	F. P.	♂	8	124	25	Hypoglycaemia	1.70	1.65	97	1.58
9.	1968 VII. 5	H. E.	♀	8	136	29	Headache	1.90	2.08	110	2.04

control children subjected to provocation with 16—132 · 100 μg of acetylcholine

$$A = VC\ 1\ (BTPS);\ B = FEV_1\ 1\ (BTPS);\ C = \frac{FEV_1 \cdot 100}{VC};\quad D = T_{\frac{1}{2}}/T_1$$

$\frac{FEV_1 \cdot 100}{VC}$	Test	−16	16−32	32−44	44−56	56−64	64−80	80−96	96−132	132− .100 μg
90	A	2.05	2.10	2.12	2.05	2.00	2.15			
	B	1.85	1.95	1.85	1.83	1.85	1.90			
	C	92	93	87	89	92	88			
	D	79	63	65	57	72	68			
100	A		2.24	2.30	2.25	2.20		2.35	2.20	
	B		2.23	2.30	2.25	2.20		2.35	2.20	
	C		100	100	100	100		100	100	
	D	80	145	116	85	76	85			
97	A		1.45		1.45				1.45	
	B		1.38		1.36				1.40	
	C		95		94				96	
	D	49	98	74	70	86		83	86	
100	A	2.85	2.80	2.94	2.85	2.92	2.84	2.90	2.85	2.55
	B	2.85	2.80	2.90	2.80	2.92	2.78	2.85	2.85	2.87
	C	100	100	99	98	100	98	99	100	97
	D		146		89	187	73	53	78	93
85	A	1.82	1.85	1.80	1.75	1.75	1.68	1.73	1.75	
	B	1.65	1.75	1.68	1.65	1.65	1.53	1.50	1.45	
	C	91	95	93	94	94	91	87	83	
	D	49	91	70	78	55		40	48	
91	A		2.73	2.70		2.85	2.87	2.85		2.92
	B		2.45	2.35		2.55	2.55	2.60		2.65
	C		90	87		90	89	91		91
	D		144	132		91		89	108	
99	A			2.51			2.48			
	B			2.40			2.32			
	C			96			94			
	D	80	78	99	71	92	117			
95	A			1.65	1.60	1.58	1.55			
	B			1.53	1.45	1.40	1.38			
	C			93	91	89	89			
	D	128	78	56	40	45	82			
97	A				2.22				1.95	
	B				2.04				1.56	
	C				92				80	
	D	86	74	67	79		54		64	

TABLE II

No.	Date of test	Initials	Sex	Age, years	Length, cm	Weight, kg	Diagnosis	Normal average	VC 1 measured	BTPS in per cents of normal	FEV_1 1 BTPS
10.	1968 VII. 8.	D. J.	♂	11	138	34	Headache	2.25	2.64	117	2.46
11.	1968 VII. 8.	R. M.	♂	10	128	27	Pyelitis	1.80	2.04	113	1.86
12.	1968 VII. 10.	B. É.	♀	13	147	52	Rectal polyp	2.40	3.32	137	3.15
13.	1968 VII. 10.	R. J.	♀	10	150	34	Check-up	2.50	2.46	95	2.28
14.	1968 VII. 11.	Sz. K.	♀	11	151	38	Pyelitis	2.60	2.85	110	2.40

1—8: spirometrically determined volumes
9—14: tachographically integrated volumes

feneau's number showed a 10% reduction and this was regarded as the criterion of a positive reaction. The lowest value of VC was reached after the second inhalation; this amounted to 26%. The percentage change of FEV_1 was similar. The capnographic changes were, however, far more pronounced; the mean decrease amounted to 25% after the first and to 57% after the second inhalation.

Analysis of the individual cases revealed the occasional presence of pathologic forms among the normal capnograms; such phenomena were, however, transient and occurred mostly in the control group. In contrast, once the reaction was positive the changes in the capnogram remained constant and there were no normal curves among the pathologic ones. This condition persisted for some time even after the inhalations. Apart from the numerical change in the value of the quotient T_2/T_1 it is precisely the regular appearance of pathological forms which characterizes the positive reaction.

The patients developed no attacks in the course of provocation since the capnogram indicated their approach in due time. Wheezing and humming sounds were heard in some previously asymptomatic cases.

cont.

$\frac{FEV_1 \cdot 100}{VC}$	Test	−16	16−32	32−44	44−56	56−64	64−80	80−96	96−132	132− . 100 μg
93	A			2.70	2.74		2.64			2.76
	B			2.37	2.30		2.19			2.37
	C			88	84		83			86
	D	68	40	69	78	87	83	73	63	78
91	A			2.10		1.92			2.07	
	B			1.86		1.68			1.74	
	C			89		88			84	
	D	73	72	78	62	38	66	92	51	80
96	A			3.30			3.34			3.36
	B			3.09			3.00			3.06
	C			83			92			91
	D	70	67	78	43	72	83	80	70	36
93	A			2.46			2.34			2.36
	B			2.28			2.22			2.13
	C			93			95			90
	D	78	137	196	72	112	79	120	75	84
84	A			2.70			2.76			3.05
	B			2.38			2.58			2.52
	C			88			93			83
	D	70	86	68	45	54	74	96	44	44

Discussion

Examination of respiration at rest. The problem of how to prevent the production of artefacts is now discussed in an increasing number of works dealing with the different methods of respiratory tests. The effect of forced expiration on volume and air flow is well documented [4, 5, 8, 9, 36, 38, 39]. Respiration at rest can be examined when measuring pulmonary flow resistance, but the necessity of oesophageal intubation prevents a routine execution of the examination and sometimes even a restoration of the rest period. Again, body plethysmography requires the patient's collaboration, and his quiet breathing especially during provocation is doubtful even if collaboration is ensured. Dealing with children, insertion of the mouthpiece may interfere with quiet breathing, a fundamental requirement of the plotting of the highly sensitive nitrogen clearance curve.

The method of bypass flow sampling means a minimum stress for the patient and is thus the most suitable procedure for creating the best conditions of quiet breathing [29].

Active collaboration — not a conditio sine qua non. This is a special problem in paediatrics which has caused a large age group to be neglected in routine examinations. Capnography requires but passive collaboration, something to which even quite young children can be habituated.

TABLE III

Spirographic and capnographic data of asthmatic children subjected to provocation with 16—132·100 μg of acetylcholine

$A = VC\ 1 \quad B = FEV_1\ 1 \quad C = \frac{FEV_1 \cdot 100}{VC} \quad D = T_2/T_1\ VC \text{ and } FEV_1 = \text{in BTPS}$

No.	Test	0	−16	16−32	32−44	44−56	56−64	64−80	80−96	96−132	132− · 100 μg
1.	A	2.40	2.25	1.78							
	B	2.23	1.80	1.25							
	C	92	80	70							
	D	148	42	19							
2.	A	1.32	0.94	0.89							
	B	1.21	0.60	0.70							
	C	92	66	78							
	D	150	35	28							
	A			0.70							
	B			0.45							
	C			64							
	D			19							
3.	A	1.06	0.70	0.98	1.35	1.30	1.30	1.10	1.02		
	B	1.04	0.70	0.96	1.02	0.90	0.90	0.84	0.90		
	C	100	100	98	74	69	69	76	88		
	D	111	94	43	41	55	41	21	33		
	A			1.10	1.05						
	B			0.82	0.95						
	C			74	90						
	D			37							
4.	A	2.38		0.85							
	B	2.10		0.60							
	C	88		71							
	D	81	79	12							
5.	A	1.90	0.82								
	B	1.85	0.71								
	C	97	86								
	D	109	37								
6.	A	2.00	2.05	1.90	1.75						
	B	1.98	1.90	1.63	1.40						
	C	99	93	87	80						
	D	40	56	31	26						
7.	A				1.30						
	B				1.02						
	C				78						
	D				15						
7.	A	1.60	1.39	1.32							
	B	1.31	1.00	0.90							
	C	82	72	68							
	D	86	40	33							
8.	A	1.28	1.00	0.97							
	B	1.13	0.85	0.61							
	C	88	85	63							
	D	31	13	8							

TABLE III cont.

No.	Test	0	−16	16−32	32−44	44−56	56−64	64−80	80−96	96−132	132− · 100 μg
9.	A	1.92	1.85	1.72	1.79	1.71	1.69				
	B	1.75	1.50	1.48	1.45	1.40	1.35				
	C	91	81	86	81	82	80				
	D	52	28	23	26	14	11				
	A				1.87						
	B				1.44						
	C				77						
	D				18						
10.	A	1.24	1.24	1.07	1.05	1.20					
	B	1.15	1.15	1.05	1.05	1.12					
	C	93	93	98	100	93					
	D	94	93	28	35	9					
	A				1.09						
	B				1.05						
	C				96						
	D				28						
11.	A	2.91		2.58	2.65	2.75	2.71	2.50			
	B	2.62		2.40	2.41	2.39	2.25	2.05			
	C	90		93	91	87	83	82			
	D	100	69	62	91	100	33	45			
	A							2.43			
	B							2.02			
	C							83			
	D							12			
12.	A	1.40		1.11							
	B	1.40		0.95							
	C	100		86							
	D	47		20							
13.	A	1.22	0.90	0.98							
	B	0.83	0.64	0.70							
	C	67	71	72							
	D	51	59	21							
14.	A	2.51		2.31	2.22		2.26	2.53	2.17		
	B	2.43		2.10	2.15		1.90	2.05	1.95		
	C	97		91	97		84	81	90		
	D	93		42	54	63	51	30	55		
15.	A	1.95		1.05							
	B	1.40		0.49							
	C	72		47							
	D	71	28	22							
16.	A	3.05		1.62							
	B	2.96		1.30							
	C	97		80							
	D	80	43	11							
17.	A	2.62		2.24							
	B	2.41		2.06							
	C	92		92							
	D	65	84	49							

TABLE III cont.

No.	Test	0	−16	16−32	32−44	44−56	56−64	64−80	80−96	96−132	132− · 100 μg
	A			2.29							
	B			2.15							
	C			94							
	D			25							
18.	A	1.87	1.72	1.78	1.69	1.78	1.74	1.58	1.80	1.42	
	B	1.72	1.68	1.66	1.62	1.65	1.55	1.45	1.55	1.25	
	C	92	98	93	96	93	89	92	86	88	
	D	62	63		80	63	71	105	34	37	
	A								1.47	1.35	
	B								1.32	1.15	
	C								90	85	
	D								33	34	
19.	A	1.22	1.32	1.11							
	B	1.16	1.26	0.93							
	C	95	95	84							
	D	76	77	24							
20.	A	2.46		1.53	1.69	1.85	1.77				
	B	1.89		1.35	1.25	1.39	0.85				
	C	80		88	74	75	48				
	D	35		22	32	31	23				
21.	A	1.67	1.49	1.41	1.52	1.63	1.61	1.61	1.60	1.59	
	B	1.55	1.25	1.10	1.50	1.55	1.22	1.30	1.20	1.35	
	C	93	84	78	100	95	76	81	75	85	
	D	50	53	55	73	55	50	65	63	64	
	A									1.52	
	B									1.45	
	C									95	
	D									96	
22.	A	2.02		1.25							
	B	2.90		1.20							
	C	94		96							
	D	83	67	45	17						
23.	A	2.20				2.17			2.26	2.24	2.05
	B					2.00			1.92	1.95	1.91
	C	92				92			85	87	93
	D	139	47	81	48	48	45	43	33	54	29
24.	A	1.94			1.21		1.80				
	B	1.75			1.05		1.55				
	C	90			87		86				
	D	46	64	67		39	29				
25.	A	1.33			1.25		0.79				
	B	1.22			1.18		0.63				
	C	92			94		80				
	D	57	51	32	45	24	16				
26.	A	3.01			3.01			3.10	2.39		2.75
	B	2.92			2.92			2.82	2.30		1.90
	C	97			97			91	96		68

TABLE III cont.

No.	Test	0	−16	16−32	32−44	44−56	56−64	64−80	80−96	96−132	132− .100 μg
27.	A	1.82			1.70	1.42	1.69	1.54			
	B	1.68			1.55	1.42	1.35	1.28			
	C	92			91	100	80	83			
	D	63	78	64	71	21	24	22			
28.	A	1.50		1.30	1.49	1.20	1.04				
	B	1.38		1.19	1.30	0.90	0.80				
	C	92		92	87	75	77				
	D	75	27	25	23	26	12				
29.	A	1.41			0.78						
	B	1.40			0.43						
	C	100			55						
	D	81	94	52	14						
30.	A	1.18				1.10		0.90		0.86	
	B	1.15				1.10		0.85		0.83	
	C	98				100		94		97	
	D	46	47	38	29	41	53	48	33	21	
31.	A	1.95		1.89		1.31					
	B	1.60		1.40		0.85					
	C	82		74		65					
	D	31	41	23	22	8					
32.	A	2.28	2.11	0.84							
	B	1.62	1.14	0.42							
	C	71	54	50							
	D	36	35	17							
33.	A	2.79			1.74						
	B	1.86			1.20						
	C	69			69						
	D	48	50	43	25						
34.	A	2.18			2.40		1.56				
	B	1.86			1.44		1.02				
	C	85			60		65				
	D	114	60	47	48	48	31				
35.	A	3.30	3.09								
	B	2.51	2.48								
	C	76	77								
	D	47	20								
36.	A	1.98		1.76							
	B	1.55		1.14							
	C	78		65							
	D	80	28	15							
37.	A	1.34			1.31						
	B	0.99			0.84						
	C	74			64						
	D	163	55	32	29						

TABLE III cont.

No.	Test	0	−16	16−32	32−44	44−56	56−64	64−80	80−96	96−132	132− · 100 µg
38.	A	2.46	2.29								
	B	1.38	1.56								
	C	56	68								
	D	40	21								
39.	A	1.98		0.84							
	B	1.43		0.54							
	C	72		64							
	D	49	25	18							
40.	A	2.53		2.51		2.19					
	B	2.28		2.22		1.80					
	C	90		88		82					
	D	90	71	88	73	24					
41.	A	2.33		2.36	2.21						
	B	1.86		1.56	1.44						
	C	80		66	65						
	D	93	40	36	33						
42.	A	3.20	3.20	3.36	3.36						
	B	2.56	2.56	2.39	2.39						
	C	80	80	71	71						
	D	52	36	44	29						
43.	A	1.81						1.53			
	B	1.50						1.19			
	C	83						78			
	D	92	69	45	20	27	41	17			
44.	A	1.82		0.84							
	B	1.20		0.43							
	C	66		51							
	D	39	29	17							
45.	A	2.93		2.24							
	B	2.46		1.56							
	C	84		73							
	D	186	94	29							
46.	A	3.36	1.20								
	B	2.22	0.66								
	C	66	55								
	D	103	17								
47.	A	1.43		1.20							
	B	1.41		0.84							
	C	99		70							
	D	44	32	10							
48.	A	3.09		3.12							
	B	204		1.56							
	C	66		50							
	D	65	29	14							
49.	A	2.09				1.74					
	B	1.86				1.23					

TABLE III cont.

No.	Test	0	−16	16−32	32−44	44−56	56−64	64−80	80−96	96−132	132− · 100 μg
	C	89				71					
	D	95	79	42	40	32					
50.	A	2.10					1.88				
	B	1.81					1.48				
	C	86					79				
	D	94	92	96	112	105	72		58		
51.	A	3.12					2.64				
	B	2.40					1.79				
	C	77					68				
	D	88	106	197	80	76	69				
52.	A	3.90			3.96	3.79					
	B	3.31			3.12	3.15					
	C	85			79	83					
	D	162	74	90	39	48					
53.	A	2.83	2.71		2.34						
	B	2.38	2.22		1.83						
	C	84	82		78						
	D	75	33	35	26						
54.	A	1.92			1.62		1.44				
	B	1.50			1.15		1.02				
	C	78			71		71				
	D	57	52	63	36	49	23				
55.	A	2.58			1.14						
	B	1.62			0.72						
	C	63			63						
	D	162	190	44	27						

Sensitivity. According to the results outlined in the foregoing, capnography represents a procedure considerably more sensitive than spirometry. This means at the same time that the number of positive reactions is higher with capnographic registration and that its reliability exceeds that of spirography.

Pathophysiological background. The following important alterations of ventilation and respiratory mechanics, characteristic of obstructive processes, have been registered in connection with asthmatic attacks: decrease of VC, MBC, FEV_1, and peak expiratory flow; increased FRC; hyperinflation; increase in total pulmonary flow resistance (R); decreased compliance; increased resistance; uneven distribution of air.

These phenomena affect gas exchange; both the physiological dead space (V_D) and the ratio $V_D : V_T$ are increased. By a simultaneous registration of the respiratory and neutral gases it was possible to demonstrate the difference between their alveolar and arterial blood levels; on the basis of such data and by means of tagged

gases light was shed on the most frequent concomitant of obstruction, the inequality between pulmonary ventilation and perfusion [12, 18].

Changes in the CO_2 contents of exhaled air were attributed by DORNHORTS et al. [10a] to the inequality of ventilation and perfusion; they recommended it many years ago for diagnosing emphysema. COMROE [7a] recommended CO_2 registration to characterize the pathologic process; HOFFBRAND [28] applied capnography for the demonstration of changes in the ventilation : perfusion ratio. LEDBETTER et al. [33] employed another method for proving the permanency of the change in cases of childhood asthma. DUBOIS et al. [11] pointed to a correlation between the rise of the plateau in the CO_2 curve and the increase of physiological dead space, while VALABHJI et al. [49] found that this correlation was more pronounced in respect of the ratio $V_D : V_T$. Inclination of the last segment, i.e. the alveolar plateau, of the capnogram is, however, due to the change in the ventilation : perfusion ratio.

It seems, therefore, that increased pulmonary resistance goes hand in hand with an increase in the proportion of hypoventilating alveolar parts including the increase of FRC. The ratio ventilation : perfusion is changed owing to decreased alveolar ventilation and especially owing to the presumable increase in pulmonary circulation produced by acetylcholine; this change is sensitively reflected by the capnographic curve. Of course, this hypothesis requires further substantiation.

Criterion of positivity. Relying on experience collected by comparison of control cases and of our knowledge of physiological fluctuations we regard the result of the present method as positive if, compared to the initial value, the ratio $T_2 : T_1$ shows a drop of more than 40%. during or after the first three inhalations of about 4400 μg of acetylcholine, or if the previously normal curve shows a permanent drop below 40%. To express positivity in per cents is preferable because absolute figures may vary with the method of evaluation.

Problems to be solved for the improvement of the method. For all its advantages our method has failed to eliminate the following sources of error in connection with respiratory provocation.

Quantity and dispersibility of the nebulized substance vary with the sprayhead employed [35].

The amount of drugs or allergens depends, besides, on alveolar ventilation, the relative value of FRC and the distribution of air, thus not merely on concentration and time which are usually indicated.

The inertness and dead space of the apparatus constitute a technical limit in the examination of infants because in such cases it does not follow prompt changes small in volume.

Examinations in the intervals between inhalations mean interruptions, and it is desirable to find means of eliminating such interruptions in cases where spirometry can be dispensed with.

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