THE USE OF CO_2 INHALATION AS A TEST OF CIRCULATION TIME [1]

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While other functions of the circulatory system have long held the attention of physiologists and clinicians, interest in the velocity of blood flow is of more recent date. Numerous investigators have established that alterations in the velocity of blood flow may be of considerable clinical significance in various pathological states, such as heart disease, hyperthyroidism, and various pulmonary conditions.

The clinical inapplicability of fluorescein, introduced by Koch (1), and of radon emanation, with which Blumgart and Weiss (2) performed valuable work on the circulation time in different segments of the vascular system, led Weiss and his colleagues to seek other substances which might be used objectively to test the rate of blood flow. Histamine was first suggested (3), the endpoint being an intense flush of the face. This method was discarded, however, because of the delayed reaction time, and the many unfavorable reactions which attended its use. Sodium cyanide, which measures the circulation time from the arm to the carotid sinus, was next introduced by Robb and Weiss (4), with respiratory stimulation as the endpoint. This method has achieved some degree of clinical application, but its use has not become general because of the alarming reactions of syncope and respiratory arrest which may occasionally occur.

Other more innocuous methods have therefore been introduced. Most of these have a subjective endpoint, which detracts from their value. All these substances, as well as cyanide and histamine, require intravenous injection, and several may produce local thrombosis and pain if extravasation takes place. They are, therefore, not very satisfactory for repeated tests. Many of these agents, in addition, have individually undesirable features. Dangerous ectopic rhythms may occur with the use of calcium salts in digitalized patients (5). Nausea and vomiting may follow the unpleasant taste induced by saccharin and decholin. Sudden death has been reported with the use of ether (6).

Ether was introduced by Hitzig (7) to distinguish "right" from "left heart time" *i.e.*, ether measures the velocity of blood flow from the antecubital veins to the pulmonary capillaries. The "left heart time" may be estimated indirectly by subtracting the ether time from the values obtained by methods which determine the arm to tongue time. The two injections are performed separately to reduce the incidence of thrombosis which nevertheless frequently occurs. The "left heart time" is of greater clinical interest, since this time is predominantly prolonged in left ventricular failure occurring as a result of rheumatic, luetic, hypertensive, coronary, or other types of heart disease (2, 3, 8).

A simple, direct, and harmless method of determining "left heart time" is available through the inhalation of CO_2. CO_2 inhalation was applied to test circulation time by Bornstein in 1912 (9). In fact, this was the first attempt to measure circulation time clinically. He, however, used only 5 to 7 per cent CO_2, and the long circulation times of 11.5 to 16.5 seconds reported by him as normal values in the few cases he studied may be attributed to the low concentration of CO_2.

TECHNIQUE

A basal metabolism apparatus from which the lime chamber has been removed serves conveniently for the performance of the test. A cylinder of CO_2 is substituted for the oxygen cylinder and sufficient CO_2 is introduced into the gas chamber to give about 4 liters of a 50 per cent mixture of CO_2 and air. After a maximal expiration to the outside the subject takes a rapid full inspiration of the CO_2 mixture through the mouth, which is immediately followed by a second rapid deep respiration to insure adequate diffusion of the gas into the alveoli. The beginning of the first in-

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spiration is considered the start of the test. The endpoint is announced subjectively by a distinct sensation of warmth passing over the head and frequently, by slight transient vertigo; and objectively by a quickening and deepening of respiration (Figure 2). The effect persists for several seconds and disappears completely within one-half minute.

The individual sensitivity to CO_2 varies considerably. In the normal subject a single inhalation of 50 per cent CO_2 is usually adequate to produce a distinct endpoint, but some subjects require stronger concentrations of CO_2 to produce a response when a single inhalation is used. Inspiration of the gas in very high concentrations acts as an irritant to many. In patients with heart disease it is frequently difficult to obtain an endpoint with single inhalations of CO_2 because of the impaired respiratory exchange due to decreased vital capacity, and delayed diffusion of gases into the alveoli resulting from decreased lung elasticity, as demonstrated by Siebeck (10). For these reasons two inhalations of 50 per cent CO_2 are routinely employed as described above.

In concentrations much below 50 per cent the endpoint becomes delayed. Thus in one subject the endpoint increased from 7 seconds with a 50 per cent mixture, to 9 seconds with a 25 per cent mixture, and to 15 seconds with a 12.5 per cent mixture. In another subject whose circulation time was 5 seconds with a 50 per cent mixture, the endpoint became similarly prolonged to 8 seconds with a 25 per cent mixture, and to 9 seconds with a 12.5 per cent mixture.

RESULTS

Values obtained in normal subjects and in pathological cases are graphically tabulated in Figure 1.

In performing repeated tests on over thirty normal subjects we found the lung to respiratory center (or possibly carotid sinus) circulation time to be much shorter than that observed by Bornstein. The normal CO_2 times ranged from 5 to 10 seconds, the majority being 7 to 8 seconds. They were constant within one second in any single individual under similar circumstances.

TABLE I

Cyanide, ether, and CO_2 times compared in the same subjects

Patient	Clinical condition	Circulation times			
		Cyanide	Ether	Cyanide-ether	CO_2
		seconds	*seconds*	*seconds*	*seconds*
S.	Hypertensive heart disease, decompensated	34	20–22	14	18
S.	Hypertensive heart disease, decompensated	31	18–20	13	16
C.	Atrophic arthritis	14	8	6	7
S.	Rheumatic heart disease, well compensated	17	8	9	8
T.	Rheumatic heart disease, well compensated	16	6	10	8
A.	Rheumatic heart disease, well compensated	15	9	6	7
W.	Rheumatic heart disease, well compensated	15	6	9	7
C.	Hypertensive heart disease, decompensated	35	20	15	18
L.	Rheumatic heart disease, decompensated	26 (saccharin)	9	17	16

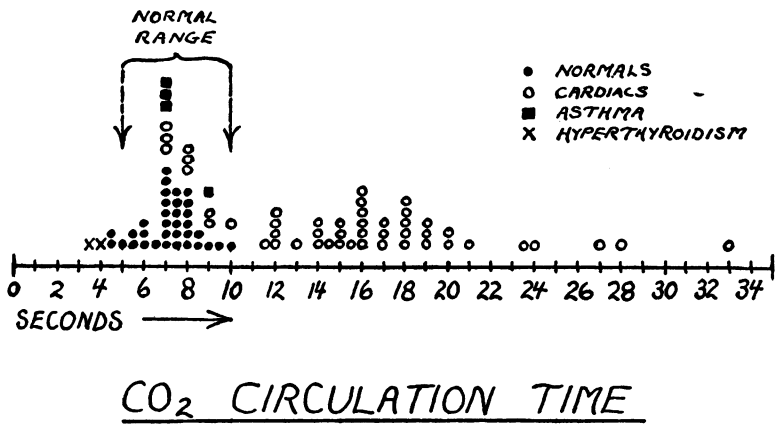

FIG. 1. CO_2 CIRCULATION TIME

These values accord well with the normal "left heart" circulation time obtained indirectly by subtracting "right heart" time (measured with ether) from combined "right and left heart" time (measured with decholin, cyanide, saccharin, or calcium salts). The latter most often ranges between 12 and 17 seconds, whereas "ether time" averages about 6 seconds, with an upper normal limit of 8 seconds. Cyanide, ether, and CO_2 times were determined in several normal and cardiac subjects. The CO_2 times corresponded almost precisely to the difference between cyanide and ether times in the same subjects (Table I). Stewart *et al.* (19) using our method, found close agreement between the CO_2 time and the difference between decholin and ether times in four subjects on whom these tests of circulation time were performed.

Figure 2 shows the effect of a single inhalation of 50 per cent CO_2 in a normal subject. Five and five-tenths seconds after inspiration, simultaneous with a subjective endpoint of warmth in the head and slight vertigo, there occurred a sharp stimulation of respiration with a marked increase in volume and rate, which subsided completely in less than one minute.

Figure 3 shows the effect in a patient with rheumatic heart disease and pulmonary congestion, whose saccharin and ether times, tested the day before, were 26 and 9 seconds respectively. After a few inhalations of 50 per cent CO_2 a subjective endpoint occurred at 16 seconds, at the point indicated by the flick in the tracing. This was followed immediately by increased ventilation. The latter was chiefly in rate rather than volume, and while definite, was not so striking as

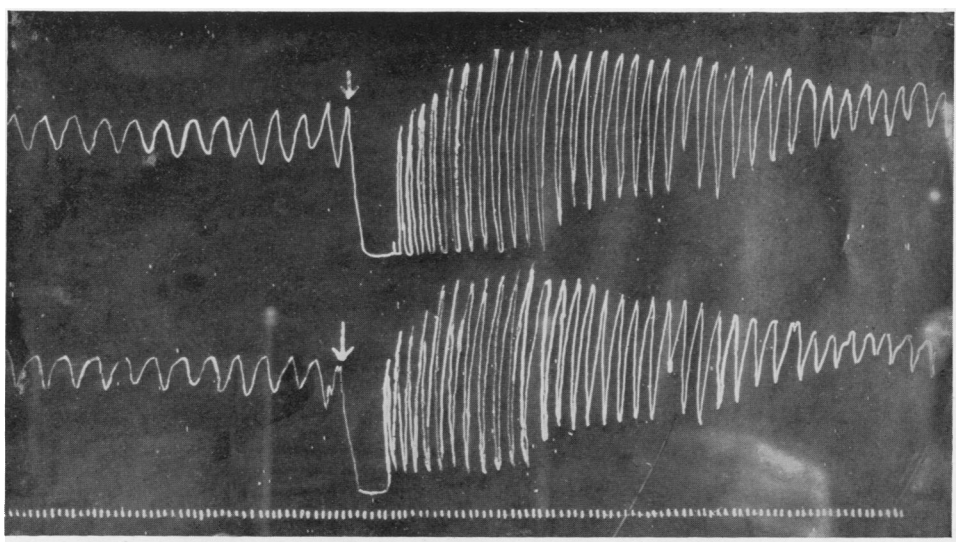

FIG. 2. INHALATION OF 50 PER CENT CO_2 IN A NORMAL SUBJECT. ENDPOINT AT 5.5 SECONDS

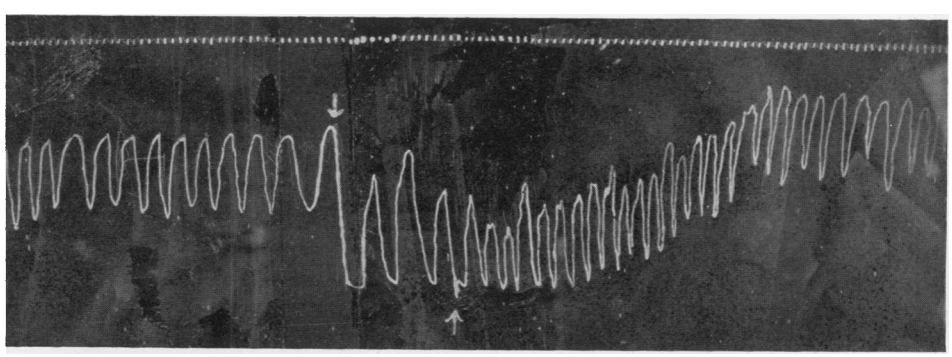

FIG. 3. INHALATION OF 50 PER CENT CO_2 IN A RHEUMATIC CARDIAC. ENDPOINT AT 16 SECONDS

in the previous tracing of the normal subject. During the period of hyperventilation the chest was held in an inspiratory position (Figure 3), a further indication of the dyspnea which the patient experienced.

Barr and Peters (11) have emphasized that the cardiac patient is unable to increase the volume of his respiration considerably because even at rest breathing is close to the maximal capacity. To quote Barr and Peters, "A normal individual with an original vital capacity of 4000 cc. may show under the stimulus of CO_2 a tidal air of 1500 to 2000 cc. In a decompensated cardiac whose vital capacity may be only 1500 cc., the tidal air will not rise above 500 to 750 cc. with maximum CO_2 stimulation. The volume of respiration is strictly limited. Any attempt to increase it is accompanied by marked subjective dyspnea."

In left heart failure of whatever cause, CO_2 times have been found distinctly prolonged, commensurate with the degree of decompensation. The longest time observed was 33 seconds. In pulmonary congestion of moderate degree the values obtained have most often been between 15 and 20 seconds. Several patients have been studied while decompensated and during recovery. Thus, one patient who entered in heart failure had a CO_2 time of 24 seconds which fell progressively with improvement to 10 seconds, remaining steady at 11 seconds up to the time of discharge. Readmitted in failure again two months later, the patient showed a CO_2 time of 22 seconds, which similarly decreased to 11.5 seconds with improvement and rose again to 17 seconds with a temporary clinical relapse. Another patient suffering from hypertensive heart disease and auricular fibrillation with heart failure had a CO_2 time of 18 seconds which fell to 13 seconds the same day after phlebotomy was performed.

Table II summarizes the changes in circulation time during recovery in eight patients who entered the hospital with congestive failure secondary to hypertensive heart disease. In all these cases the CO_2 times were initially prolonged and fell toward normal coincident with improvement. The shortening of the circulation time was closely related to the clinical course.

Normal values of 7 to 10 seconds have been found in well compensated cases of heart disease.

TABLE II

CO_2 circulation times in patients with heart failure and during recovery (hypertensive heart disease)

Patient	Date	CO_2 time	Clinical condition
	1937–1938	*seconds*	
N.	November 10	24	Decompensated, pulmonary edema, auricular fibrillation
	November 11	15	Markedly improved
	November 12	10	Improved
	November 18	11	Out of bed
P.	November 11	18	Pulmonary edema, before phlebotomy
	November 11	13	After phlebotomy
	November 15	14	
McN.	March 25	27	Congestive failure, basal râles, enlarged liver, edema
	March 29	28	Unchanged
	March 31	23	Improved, râles persist, liver slightly enlarged, no edema
	April 4	16	Improved, few râles, liver not felt, no edema
	April 8	9	Well, out of bed
S.	March 29	20	Congestive failure, basal râles, enlarged liver, edema
	March 31	15	Improved, basal râles
	April 4	15	Basal râles
	April 8	12	Improved, occasional râle
K.	March 31	14	Congestive failure, auricular fibrillation, râles, enlarged liver, edema
	April 8	10	Out of bed, no râles
B.	March 31	16	Decompensated, basal râles, weight 118 lbs.
	April 4	15	Basal râles, weight 111 lbs.
	April 8	12	Occasional basal râle
J.	March 31	18	Decompensated, basal râles, enlarged liver, edema, weight 166 lbs.
	April 4	14	Improved, basal râles, weight 145 lbs.
	April 8	12	Compensated, weight 138 lbs.
R.	March 31	20	Decompensated, basal râles, enlarged liver, edema
	April 4	15	Basal râles, enlarged liver
	April 8	12	Occasional basal râle

In one case with ascites and edema finally diagnosed as portal cirrhosis, in which at first the differential diagnosis from heart disease was difficult, the CO_2 time was normal being 7 to 8 seconds. Four asthmatic patients without heart disease had normal CO_2 times, three being 7 seconds and one 9 seconds. This group is of particular interest since the circulation time was normal despite a considerable diminution in vital capacity. The prolonged time in heart disease cannot therefore be attributed to a delayed diffusion of gas into the alveoli, since conditions of impaired respiratory exchange exist in asthma, and the circulation time is nevertheless normal.

An interesting experience was the finding of an unusually rapid CO_2 time of 4 seconds in a patient who had auricular fibrillation with a very rapid ventricular rate. This led to the suspicion of hyperthyroidism, and further history disclosed the development of symptoms of Graves' disease following a severe psychic trauma a few months

before. Basal metabolic determinations were repeatedly + 60, and at operation a toxic diffuse goiter was found. With clinical improvement and a decrease in metabolism to + 12 following thyroidectomy the CO_2 time became prolonged to 9 seconds, more than double its original value. Another patient, convalescing on a surgical ward from a laceration of the foot, was tested as a supposed normal and was also found to have an unusually rapid CO_2 time of 3.5 seconds. A more careful history and physical examination, together with repeatedly high basal metabolic rates also led to a diagnosis of hyperthyroidism, previously unsuspected.

DISCUSSION

CO_2 inhalation is apparently entirely harmless, being but a temporary exaggeration of a physiological stimulant. There is some question as to whether the stimulation of respiration is due to a direct action of CO_2 on the respiratory center or on the carotid sinus. Although anoxemia has been proven by Heymans (12) to stimulate respiration solely through the chemical receptors in the carotid sinus, CO_2 probably acts directly on the respiratory center as well as on the carotid sinus (13); and such authorities as Haldane and Priestley (14) conclude that "the reflex control of breathing by chemical stimulation of the carotid nerve endings has not been established, at any rate as regards CO_2." The brief inhalation of concentrated CO_2 does not appear to have any deleterious effect on the circulation. Berencsy (15) found no change in the electrocardiograms of dogs during short periods of respiration of pure CO_2, apart from a transient sinus bradycardia which he attributed to a trigeminovagal reflex. Prolonged respiration of CO_2, as Grollman (16) and others have shown, may increase the cardiac output significantly.

Transient vertigo frequently occurs which may be due either to a sudden rise in intracranial pressure, or to the anesthetic action of CO_2, as it is an anesthetic in high concentration.

Apart from the subjective dyspnea and vertigo, there are other sensations produced by CO_2 inhalation which afford distinct endpoints. Thus there is regularly felt a transient warmth and fullness passing over the head, and frequently there is a visible flush of the face. The sensation of warmth and fullness in the head is probably due to a direct vasodilating action of CO_2 on the cerebral blood vessels. This view is supported by an experiment in which manometric readings were made of spinal fluid pressure during inhalation of CO_2. The patient suffered from cardiac decompensation due to hypertensive heart disease. The initial spinal fluid pressure was 24 cm. H_2O. After a single deep inhalation of CO_2 it remained unchanged until 17 seconds later when, simultaneous with subjective and objective endpoints, the spinal fluid pressure rose several cm. of H_2O with each systole, to a height of 40 cm. at about 40 seconds, after which it declined to its original level within one minute. With continuous breathing of 30 per cent CO_2 the spinal fluid pressure similarly began to rise abruptly with the subjective and objective endpoints at 17 to 18 seconds and within 1½ minutes attained 60 cm. H_2O at which time the patient experienced marked distress and hyperpnea. Inhalation of CO_2 was discontinued at this time and the pressure fell to its initial level of 24 mm. within 2 minutes. A control period of voluntary hyperpnea did not significantly alter the spinal fluid pressure, so that the marked rise may be attributed to the vasodilating action of CO_2, with increased cerebral blood flow. Bouckaert and Jourdan (17), Schmidt (18), and several other investigators have likewise demonstrated a direct vasodilating action of CO_2 on the cerebral blood vessels by other methods.

The slight flush of the face which is sometimes observed normally is much more striking in hyperthyroidism. In the two cases of hyperthyroidism already referred to there was an intense flush of the face and a sensation of warmth over the entire body followed by profuse sweating. This reaction disappeared in one patient who had a thyroidectomy with the return of basal metabolism to normal. In another patient with cardiac decompensation of uncertain etiology a marked reaction of this sort gave the first clue of a hyperthyroid state.

SUMMARY

CO_2 inhalation may be employed clinically to estimate circulation time. The CO_2 test measures "left heart" time (lung to respiratory center). Its advantages are that it is a physiological respiratory stimulant; it is entirely harmless; the effect

is transitory; it does not require injection, and it may be used repeatedly in the same subject.

The circulation time, by this method, is prolonged in heart disease commensurate with the degree of left heart failure. Normal values range from 5 to 10 seconds and correspond closely to the expected results according to the cyanide and ether times.

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