THE VENTILATORY RESPONSE TO CARBON DIOXIDE IN MITRAL DISEASE*

BY

H. G. PAULI, F. E. NOE, AND E. O. COATES

*From the Medizinische Poliklinik, Berne University, Berne, Switzerland,
and the Henry Ford Hospital, Detroit, Michigan, U.S.A.*

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As long as ventilatory studies were the only approach to the problem of dyspnoea in cardiac patients, its explanation seemed to be found in pulmonary changes secondary to congestive failure (Peabody and Wentworth, 1917). Combined ventilatory and circulatory measurements in such patients showed the problem to be more complex. Reduced ventilatory capacity appears to become a significant factor in advanced left-sided failure only (West *et al.*, 1953). In cases without gross congestive failure, the diminution of cardiac output interfering with a normal metabolic exchange to the peripheral tissue—including the respiratory centre—and the rise of pressure in the pulmonary vascular system institute an increased ventilatory demand. An increased ventilatory drive manifests itself in a raised total ventilation during rest and exercise. The sensitivity of the respiratory centre to its major stimulus (Nielsen, 1936), the arterial CO_2 tension, should therefore be increased. By introducing exogenous hypercapnia under CO_2 inhalation and correlating different levels of arterial PCO_2 with their corresponding levels of total ventilation graphically, a stimulus response curve will be obtained. This relation has been shown to be linear within the range of physiological stimulation and response (Alexander *et al.*, 1955; Julich, 1953; Nielsen, 1936; and Schäffer, 1949) (Fig. 1). The responsiveness of the centre is defined by the increment in ventilation produced by a

FIG. 1.—Theoretical CO_2 -stimulus-response-relationship (see text). The line below the resting ventilation (V) is extrapolated.

given increment in PaCO_2 : $\Delta \dot{V} / \Delta \text{PaCO}_2$ ("quotient of responsiveness," QR) or the slope ($\text{tg} \alpha$) of the resulting line. The extrapolated intersection of this line with the abscissa represents the level of PaCO_2 reduction at which the CO_2 -stimulus presumably becomes ineffective in producing any

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ventilatory response or the theoretical central threshold for the CO_2 -stimulus (P_0). At any higher level of arterial PCO_2 (P) the actual CO_2 -stimulus ($P - P_0$) is responsible for the level of ventilation (V). Responsiveness, as defined above, can be considered as the relation between ventilation and actual CO_2 -stimulus or:

$$\begin{aligned} \text{tg}\alpha &= V/P - P_0 \\ \text{therefore} \quad P - P_0 &= V/\text{tg}\alpha \\ \text{and} \quad P_0 &= V/\text{tg}\alpha \\ \text{and finally} \quad V &= \text{tg}\alpha(P - P_0). \end{aligned}$$

In other words, *actual ventilation is the product of responsiveness of the respiratory centre and the actual CO_2 stimulus*. Hyperventilation at a given level of arterial PCO_2 can therefore be explained either by an increased responsiveness or a decreased central threshold for the arterial PCO_2 . In a large group of cardiac patients, Julich (1953) has found steeper stimulus response curves in comparison with normal subjects.

METHODS AND RESULTS

We have used a rebreathing method, eliminating anoxic stimulation by accumulating CO_2 in pure oxygen. In this manner we have examined a group of patients with rheumatic heart disease amenable to surgical treatment and with no signs of congestive failure at the time of study. The time interval between the active rheumatic disease or onset of cardiac symptoms and the study was in all cases more than ten years. This report concerns the findings in a sub-group of 7 patients with pure or predominant mitral stenosis (Table I). As we found a small but significant rise of the average total ventilation above the normal in this group (from 4.65 to 5.02 l./min./m.²BSA), we expected the respiratory responsiveness to be raised, that is, the stimulus response curve to be steeper than in normal subjects. Instead, it was found to be flattened (Fig. 2). The quotient

TABLE I
VENTILATION AND ARTERIAL BLOOD STUDIES

	Age	Lesion	Functional classifica- tion*	Resting ventila- tion VI l./ min./m. ²	Arterial blood studies			
					pH	Resting CO ₂ tension mm. Hg	PCO ₂ thresh- hold mm.Hg	Quotient of respon- siveness l./min./m. ²
under 100% O ₂	under room air	under O ₂ -inhalation and CO ₂ -accumulation						
Patients with rheumatic lesions:								
R.U.	51	MS& MR	III	5.22	7.43	32.5	22.0	0.56
E.E.	52	MS& MR	III	5.06	7.46	33.0	23.0	0.52
H.E.	43	MS	II-III	5.10	7.40	39.0	32.0	0.86
I.C.	46	MS	II	4.76	7.41	37.6	31.0	0.64
P.K.	28	MS	II	4.48	7.41	35.0	31.0	1.14
G.K.	32	MS	II	5.36	7.42	36.5	25.0	0.55
I.S.	49	MS	II	5.14	7.40	40.5	34.0	0.81
Average of 7 patients	43.1			5.02	7.42	36.3	28.3	0.73
Average values of 11 normal subjects	36.6			4.65	7.41	39.9	35.5	1.12
Post-operative values:								
G.K.	32			4.82	7.42	36.8	34.0	1.61
I.S.	49			4.14	7.40	42.0	40.0	1.79

* According to the specification by the New York Heart Association.

MS = mitral stenosis.

MR = mitral regurgitation.

FIG. 2.—Average stimulus-response curve in patients with mitral valvular lesions. The arrows indicate level of resting ventilation.

of responsiveness, comparing the increase in ventilation in $l./m.^2$ BSA with the increase in arterial CO_2 tension in millimetres of mercury, is reduced from 1.12 in the controls to 0.73 in these patients. This decrease is statistically highly significant ($p < 0.01$). The arterial PCO_2 is reduced (average 36.3 mm. compared with 39.9 mm. Hg in the controls) and still total ventilation is raised above normal. This seems to be effected by a reduction of the central threshold to the arterial PCO_2 from 35 mm. in the controls to 28 mm. Hg, despite the lowered responsiveness. The flattening of the stimulus response curve recalls the findings in patients with pulmonary emphysema (Alexander *et al.*, 1955; Julich, 1953; Pauli *et al.*, 1958). In emphysematous patients, however, arterial PCO_2 levels tend to be raised. Chronic CO_2 accumulation has been held responsible for the decrease

FIG. 3.—Average stimulus-response curve of two patients with mitral stenosis before and after commissurotomy. I before, and II after, operation.

in the respiratory responsiveness in these cases (Alexander *et al.*, 1955). In contrast, we have here a clinical entity where decreased respiratory responsiveness is connected with a low arterial CO₂ tension.

Two of our patients were re-examined, 111 and 84 days respectively, after successful mitral valvotomy. In both of them the stimulus response curves were altered in the same sense (Table I) and are therefore averaged in Fig. 3. They show a complete, even overshooting, reversion of the pre-operative deviation from normal. Responsiveness is more than doubled (from 0.68 to 1.70 l./min./m.²/mm. Hg) and the central PCO₂ threshold is raised from 32 to 39 mm. Hg, while total ventilation is normal (5.25 l./min./m.² before, and 4.48 l./min./m.² BSA after operation).

DISCUSSION

As Krogh and Lindhard (1913) have already pointed out in the case of muscular hyperpnoea, the changes in ventilation observed here are not due to an alteration of the respiratory *stimulus* but to one of the respiratory *centre*, namely its responsiveness and threshold level. Up to the present the mechanisms responsible for these changes are only a matter of speculation. There is strong evidence that besides chemical influences, such as arterial CO₂ tension (Schäffer, 1949), H-ion concentration, and bicarbonate levels (Nielsen, 1936), reflex mechanisms originating from the musculo-skeletal system and the thoracic organs (as in muscular exercise (Comroe and Schmidt, 1943; Dejours *et al.*, 1956; and Pauli *et al.*, 1958) or from extra-cerebral chemoreceptors (as in anoxia (Luft, 1941; Opitz, 1941)) determine the responsiveness of the centre. Arterial bicarbonate levels are somewhat diminished in our patients in comparison with normal subjects, but we have no evidence whether this phenomenon is primary or secondary to hyperventilation. It seems unlikely that H-ion concentration is considerably altered in the tissue of the respiratory centre, the arterial values being normal. No anoxic factor can be presumed, judging from arterial blood determinations. Oxygen transport and tissue CO₂ and H-ion concentration may on the other hand be altered by a diminished cardiac output. From all the data available up to now, it appears highly probable that multiple factors are responsible for the changes in reactivity of the respiratory centre in these cardiac patients.

SUMMARY

The regulation of ventilation in 7 patients with pure or predominant rheumatic mitral stenosis was investigated by measuring respiratory response to increasing CO₂-content of the inspired gases. Respiratory responsiveness, as defined by increase in specific ventilation produced by a given increase in arterial CO₂-tension, was found to be significantly lowered in comparison with 11 normal subjects. On the other hand, the extrapolated central threshold value for the arterial CO₂-tension was diminished in these patients, resulting in a slight rise of ventilation at the level of resting arterial PCO₂.

Two patients were studied before, and 84 and 111 days respectively after, successful mitral valvotomy. Their respiratory response was found to be increased after operation, while the central arterial PCO₂ threshold was raised.

The possible mechanisms of these changes in respiratory regulation are discussed.

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